Waist Circumference and All-Cause Mortality in a Large US Cohort

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Background: Waist circumference (WC), a measure of abdominal obesity, is associated with higher mortality independent of body mass index (BMI). Less is known about the association between WC and mortality within categories of BMI or for the very high levels of WC that are now common.

Methods: We examined the association between WC and mortality among 48 500 men and 56 343 women, 50 years or older, in the Cancer Prevention Study II Nutrition Cohort. A total of 9315 men and 5332 women died between 1997 and the end of follow-up in 2006.

Results: After adjustment for BMI and other risk factors, very high levels of WC were associated with an approximately 2-fold higher risk of mortality in men and women (among men, relative risk [RR] = 2.02; 95% confidence interval [CI], 1.71-2.39 for WC ≥120 cm compared with <90 cm; among women, RR = 2.36; 95% CI, 1.98-2.82 for WC ≥110 cm compared with <75 cm). The WC was positively associated with mortality within all categories of BMI. In men, a 10-cm increase in WC was associated with RRs of 1.16 (95% CI, 1.09-1.23), 1.18 (95% CI, 1.12-1.24), and 1.21 (95% CI, 1.13-1.30) within normal (18.5 to <25), overweight (25 to <30), and obese (≥30) BMI categories, respectively. In women, corresponding RRs were 1.25 (95% CI, 1.18-1.32), 1.15 (95% CI, 1.08-1.22), and 1.13 (95% CI, 1.06-1.20).

Conclusion: These results emphasize the importance of WC as a risk factor for mortality in older adults, regardless of BMI.

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A LARGE WAIST CIRCUMFERENCE (WC) has been associated, independent of body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), with higher circulating levels of inflammatory markers,[1,2] insulin resistance,[3,4] type 2 diabetes mellitus,[5-7] dyslipidemia,[7,8] and coronary heart disease.[9,10] The WC may be associated with these conditions because it is strongly correlated with visceral adipose tissue,[11,12] which is thought to be more pathogenic than subcutaneous adipose tissue.[12,13]

Relatively consistent evidence now shows that a larger WC is associated with higher mortality. Among prospective studies that included 1000 or more deaths,[14-24] all but 2[18,24] found a statistically significant positive association between WC and mortality, although the strength of the association varies. Six of these studies[16,17,20-23] demonstrated that WC remained associated with mortality even after adjustment for BMI. Two important areas of uncertainty remain, however, about the association between WC and mortality. First, risks have not been well quantified for very large WCs that substantially exceed the clinically defined threshold for abdominal obesity (≥88 cm in women and ≥102 cm in men).[25] Quantifying these risks is important because more than 50% of men and 70% of women in the United States between the ages of 50 and 79 years now exceed the WC threshold for abdominal obesity.[26] Second, few studies have examined the association between WC and mortality within categories of BMI. Understanding how WC is associated with risk of mortality within normal, overweight, and obese categories of BMI may be useful in determining when the measurement of WC could provide meaningful information beyond that provided by BMI.

We examined the association between WC and risk of mortality in the Cancer Prevention Study II (CPS-II) Nutrition Cohort, a large prospective study of predominantly older adults. We focused on examining associations with very high levels of WC and within standard categories of BMI.

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METHODS

STUDY COHORT

Men and women in this analysis were drawn from the 184 190 participants in the CPS-II Nutrition Cohort, established in 1992 and described in detail elsewhere.[27] The CPS-II Nutrition Cohort is a subset of the larger CPS-II Cohort established by the American Cancer Society in 1982. All aspects of the CPS-II Nutrition Cohort study protocol were approved by the Emory University Institutional Review Board.

At enrollment in 1992 or 1993, participants completed a mailed 10-page self-administered questionnaire that included information on demographic, medical, and behavioral factors. The WC was first ascertained on the 1997 follow-up questionnaire, which also collected updated information on current weight, smoking status, and other health-related factors. Participants were provided with a tape measure and asked to measure their WC just above the navel to the nearest quarter inch, while standing, and to avoid measuring over bulky clothing. The validity of self-reported WC was not directly assessed in this cohort, although self-measured WC was documented to be reasonably accurate in other study populations.[28,29] Hip circumference was not measured. The BMI was calculated from weight reported on the 1997 survey and height reported on the 1982 survey.

A total of 73 047 men and 87 259 women from the CPS-II Nutrition Cohort completed the 1997 follow-up survey. Of these, we excluded participants with missing information on WC (9485 men and 14 015 women) or BMI (4944 men and 5770 women), extreme or implausible WC values (≤20 in or ≥75 in, which corresponds to ≤51 cm or ≥190 cm; 15 men and 58 women), underweight BMI or extreme BMI (<18.5 or >60; 413 men and 1654 women), or unknown smoking status (785 men and 607 women). To reduce bias from disease-related weight loss, we excluded participants with a weight loss of 10 lbs or more (≥4.5 kg) between the 1992 and 1997 surveys (7997 men and 7482 women). We also excluded participants with a weight gain of more than 25 lbs (>11.3 kg) between the 1992 and 1997 surveys (907 men and 1193 women) because their reported weight in 1997 may not have been representative of their long-term weight. To focus specifically on older adults, we excluded the small number of participants who were younger than 50 years at the time they completed the 1997 questionnaire (1 man and 137 women). A total of 48 500 men and 56 343 women remained for analysis.

MORTALITY FOLLOW-UP

Vital status and cause-of-death codes were obtained through automated linkage of all cohort participants with the National Death Index.[30] Mortality follow-up was completed through December 31, 2006. Death certificates or codes for cause of death were obtained for 99.3% of known deaths. Causes of death were classified using the *International Classification of Diseases, Ninth Revision* (*ICD-9*)[31] for deaths occurring from 1992 through 1998 and the *Tenth Revision* (*ICD-10*)[32] for deaths occurring from 1999 through 2006. Specific causes of death were grouped into 4 broad categories: cardiovascular disease (*ICD-9* codes 390-459, *ICD-10* codes I00-I99), cancer (*ICD-9* codes 140-208 and 199-208, *ICD-10* codes C00-C97), respiratory disease (*ICD-9* codes 460-519, *ICD-10* codes J00-J98), and all other causes.

STATISTICAL ANALYSES

The WC was categorized using 5-cm increments. For analyses that required stratification by BMI or other factors, we created categories using 10-cm increments. A continuous variable for WC was used when calculating *P* values for trend.

Cox proportional hazards models were used to calculate relative risk (RR) estimates associated with all-cause or cause-specific mortality. We used follow-up time since completion of the 1997 questionnaire as the time axis.

All proportional hazards models were adjusted for age (using the stratified Cox procedure with 1-year age strata[33]), race (white, black, other, or unknown), educational level (less than high school, high school graduate, some college, college graduate, graduate school, or unknown), physical activity (<7, 7 to <14, 14 to <21, or ≥21 metabolic equivalents per week, or unknown), smoking status (never smoker, cigar/pipe smoker only, former cigarette smoker [subcategorized by years since quit: <5, 5 to <10, 10 to <20, 20 to <30, ≥30, or unknown], or current cigarette smoker [subcategorized by years smoked: ≤40, >40, or unknown]), height (men: <69 in, 69 to <70 in, 70 to <72 in, or ≥72 in; women: <63 in, 63 to <64 in, 64 to <66 in, or ≥66 in), marital status (married, widowed, divorced or separated, never married, or unknown), and alcohol use (never, <1 drink per day, 1 drink per day, >1 drink per day, former drinker, or unknown). Models in women were also adjusted for hormone therapy (never, former, current, or unknown). Models adjusted for BMI included variables for BMI categories (18.5 to <20, 20 to <22.5, 22.5 to <25, 25 to <27.5, 27.5 to <30, 30 to <32.5, 32.5 to <35, or ≥35) and cross-product interaction terms between the variables for each BMI category and age at baseline (<70 years or ≥70 years). Including BMI-by-age interactions may better adjust for BMI because the association between BMI and mortality differs substantially by age.[34,35]

We did not adjust for health conditions (eg, hypertension, diabetes, cardiovascular disease, cancer, or respiratory disease) to avoid controlling for conditions that are intermediates on the causal pathway between obesity and mortality.[34]

We examined whether the association between WC and risk of mortality varied by age at baseline (<70 years or ≥70 years), history of diabetes, smoking status (never, current, or former), physical activity (<7 or ≥7 metabolic equivalents per week), follow-up time (continuous), or a history of 1 or more diseases that could potentially result in both weight loss and increased risk of mortality (cardiovascular disease, cancer, or respiratory disease). Additionally in women, we examined whether the association between WC and risk of mortality varied by use of hormone therapy (never, former, or current). Specifically, we modeled multiplicative interaction terms between WC (categorized in **Table 1**) and each potential effect measure modifier (categorized as dichotomous or continuous, as noted previously) and calculated a *P* value for interaction by comparing the likelihood ratio statistic from models with and without interaction terms.[36]

Age-standardized mortality rates were calculated to provide a measure of absolute risk. Mortality rates were standardized to the age distribution of person-years contributed by men or women in this analysis.

RESULTS

Participants were predominantly white and 55 years or older, regardless of WC (Table 1). The median age at baseline was 69 years in men and 67 years in women. Men and women in the highest category of WC were more likely than those with smaller waists to be less educated, to have a high BMI, to be physically inactive, to be former smokers, and to have a history of cardiovascular disease, cancer, or respiratory disease. The age-adjusted correlation coefficient for BMI and WC was 0.79 in men and 0.80 in women.

The RRs for all-cause mortality associated with categories of WC appear in **Table 2** and are illustrated

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Table 1. Baseline Characteristics of Study Participants by Waist Circumference, Cancer Prevention Study II Nutrition Cohort, 1997[a]

Characteristic	Waist Circumference, cm								
	Men				Women				
	<90 (n=8429)	90 to <100 (n=20 601)	100 to <110 (n=13 569)	≥110 (n=5901)	<75 (n=11 303)	75 to <85 (n=16 886)	85 to <95 (n=15 138)	95 to <105 (n=8446)	≥105 (n=4570)
Age, y, %									
50-54	0	0	0	0	3	2	1	2	2
55-59	4	4	3	4	14	11	9	9	11
60-64	23	21	20	24	27	25	23	23	23
65-69	29	29	30	31	27	29	29	28	28
70-74	27	29	30	29	19	22	24	25	23
≥75	17	17	17	13	10	12	13	14	13
Race, %									
White	96	98	99	98	97	98	98	98	98
Black	1	1	1	1	1	1	1	1	1
Other or unknown	3	1	1	1	2	1	1	1	1
Educational level, %									
<High school	5	6	7	9	3	4	4	5	6
High school graduate	15	17	19	21	27	28	32	35	35
Some college	24	24	26	27	32	32	32	31	32
College graduate	23	24	23	21	23	22	19	17	15
Graduate school	32	28	25	22	15	14	12	11	11
Unknown	1	1	1	1	1	1	1	1	1
BMI, %									
18.5 to <25.0	83	43	9	1	95	73	32	9	1
25.0 to <30.0	17	55	71	33	5	26	58	51	21
30.0 to <35.0	0	2	19	50	0	1	10	35	41
≥35.0	0	0	1	16	0	0	1	6	36
Physical activity, metabolic equivalents per week, %									
<7	18	21	28	39	18	23	29	36	47
7 to <14	24	29	30	28	29	32	32	31	29
14 to <21	28	29	26	21	29	26	24	21	15
≥21	28	19	14	9	22	18	13	10	7
Unknown	2	2	3	3	1	2	2	2	3
Smoking status, %									
Never	35	30	24	23	56	54	54	55	53
Current cigarette smoker	6	5	5	4	5	5	5	5	4
Former cigarette smoker	54	60	66	69	40	41	42	40	43
Cigar/pipe smoker only	5	6	6	5	NA	NA	NA	NA	NA
History of cardiovascular disease, %[b]	23	25	26	27	8	9	11	12	15
History of cancer, %	16	17	18	18	16	16	17	17	19
History of respiratory disease, %[c]	9	8	9	12	8	8	9	10	12

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, women were not asked about cigar or pipe smoking.

[a] Percentages were standardized to the age distribution of men or women in the cohort. Some percentages do not total 100 owing to rounding.

[b] History of stroke and/or heart disease.

[c] History of emphysema, chronic bronchitis, or other lung disease.

graphically in the **Figure**. Before adjustment for BMI, WC was associated with statistically significant increases in mortality only at levels of 110 cm or more among men and 95 cm or more among women. After adjustment for BMI, all levels of WC higher than the lowest level were associated with higher mortality, and the RR estimates increased approximately linearly with increasing WC in men and women ($P < .001$).

We also calculated RRs adjusted for BMI using the clinically recommended cut points for abdominal obesity (≥102 cm in men and ≥88 cm in women).[25] Among men, a WC of 102 cm or more was associated with an RR of 1.17 (95% confidence interval [CI], 1.10-1.23) compared with a WC of less than 102 cm. Among women, a WC of 88 cm or more was associated with an RR of 1.23 (95% CI, 1.14-1.32) compared with a WC of less than 88 cm.

The association between BMI and risk of mortality, with and without adjustment for WC, is shown in a supplementary table (eTable; http://www.archinternmed.com). Before adjustment for WC, risk of mortality was increased at both the lowest and highest BMI levels. After adjustment for WC, high levels of BMI were no longer associated with increased risk of mortality, although adjustment for WC may substantially alter the interpretation of BMI by causing BMI to reflect lean body mass more than adiposity.[37]

The association between WC and risk of mortality within categories of BMI is provided in **Table 3**. In men and women, WC was positively associated with higher

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Table 2. All-Cause Mortality by Waist Circumference (WC), Cancer Prevention Study II Nutrition Cohort, 1997-2006

WC, cm	Deaths/ Person-Years	Rate[a]	Age-Adjusted RR (95% CI)	Multivariate-Adjusted RR (95% CI)[b]	Multivariate- and BMI-Adjusted RR (95% CI)[c]
Men					
<90	1469/71 011	2080	1 [Reference]	1 [Reference]	1 [Reference]
90 to <95	1808/83 844	2144	1.03 (0.97-1.11)	1.01 (0.94-1.08)	1.15 (1.06-1.24)
95 to <100	1847/89 334	2026	0.98 (0.91-1.05)	0.92 (0.86-0.98)	1.11 (1.03-1.21)
100 to <105	1551/65 089	2364	1.15 (1.07-1.23)	1.04 (0.97-1.12)	1.32 (1.21-1.44)
105 to <110	1213/47 663	2502	1.22 (1.13-1.31)	1.05 (0.97-1.14)	1.38 (1.25-1.53)
110 to <115	712/26 101	2801	1.38 (1.26-1.50)	1.16 (1.06-1.27)	1.55 (1.38-1.75)
115 to <120	349/11 526	3293	1.61 (1.43-1.81)	1.33 (1.18-1.50)	1.80 (1.55-2.09)
≥120	366/10 618	4040	2.04 (1.82-2.28)	1.55 (1.38-1.75)	2.02 (1.71-2.39)
Women					
<75	803/100 123	888	1 [Reference]	1 [Reference]	1 [Reference]
75 to <80	658/67 954	1002	1.14 (1.03-1.26)	1.08 (0.98-1.20)	1.24 (1.11-1.38)
80 to <85	724/81 022	889	1.01 (0.91-1.12)	0.94 (0.85-1.04)	1.17 (1.05-1.31)
85 to <90	819/73 507	1076	1.23 (1.11-1.35)	1.10 (1.00-1.22)	1.48 (1.32-1.67)
90 to <95	667/58 929	1069	1.21 (1.10-1.35)	1.05 (0.94-1.16)	1.47 (1.29-1.67)
95 to <100	558/44 031	1209	1.37 (1.23-1.52)	1.16 (1.04-1.29)	1.68 (1.46-1.93)
100 to <105	396/29 351	1279	1.46 (1.30-1.65)	1.19 (1.05-1.34)	1.74 (1.49-2.03)
105 to <110	278/17 413	1539	1.75 (1.52-2.00)	1.37 (1.19-1.58)	1.98 (1.66-2.36)
≥110	429/21 608	2006	2.31 (2.05-2.59)	1.72 (1.53-1.95)	2.36 (1.98-2.82)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; RR, relative risk.
[a] Mortality rate per 100 000 person-years, standardized to the age distribution of men or women in the cohort.
[b] Adjusted for age, race, educational level, marital status, smoking status, alcohol use, height, and physical activity. Models for women were also adjusted for hormone therapy.
[c] Additionally adjusted for BMI.

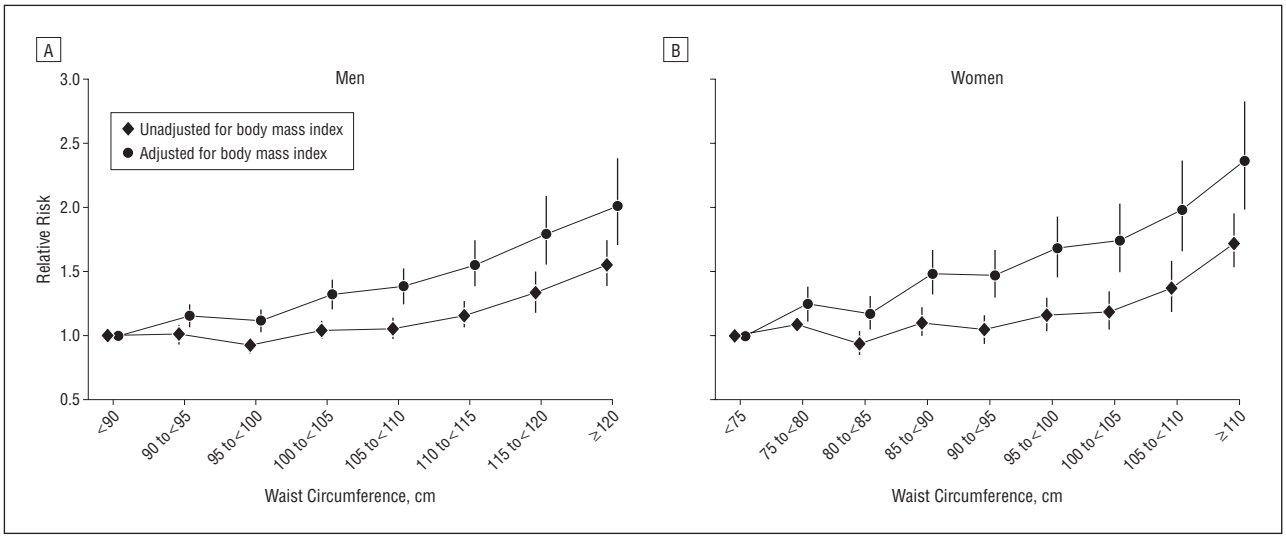

Figure. All-cause mortality by waist circumference in the Cancer Prevention Study II Nutrition Cohort, 1997-2006. Models were adjusted for age, race, educational level, marital status, smoking status, alcohol use, height, and physical activity. Models for women were also adjusted for hormone therapy.

risk of mortality within all categories of BMI. In women, higher levels of WC were more strongly associated with mortality among those in the normal BMI category (18.5 to <25) than among women who were overweight or obese (P=.03 for interaction by BMI category). In men, the association between WC and mortality did not vary significantly by BMI (P=.56 for interaction by BMI category). Within categories of BMI, age-standardized mortality rates increased with increasing levels of WC. In contrast, within categories of WC, mortality rates did not increase with increasing levels of BMI.

We found no statistically significant interactions between WC (adjusted for BMI) and smoking, diabetes, or follow-up time in men or women. Among women, we also found no interaction between WC and hormone therapy. However, RRs associated with WC were lower among women with a history of a disease potentially related to weight loss (cancer, cardiovascular disease, or respiratory disease) than among those without (P=.004 for interaction) (**Table 4**). Among men, RRs associated with WC were lower among those younger than 70 years at baseline than among men 70 years or older (P=.003 for inter-

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Table 3. All-Cause Mortality by Waist Circumference (WC) Within Categories of BMI, Cancer Prevention Study II Nutrition Cohort, 1997-2006

	BMI, 18.5 to <25 (Normal)			BMI, 25 to <30 (Overweight)			BMI, ≥30 (Obese)		
WC, cm	Deaths/ Person-Years	Rate[a]	RR (95% CI)[b]	Deaths/ Person-Years	Rate[a]	RR (95% CI)[b]	Deaths/ Person-Years	Rate[a]	RR (95% CI)[b]
Men									
<90	1284/58 540	2111	1 [Reference]	181/12 275	1813	1 [Reference]	4/196	NC	NC
90 to <100	1911/72 792	2257	1.14 (1.05-1.23)	1691/95 977	1910	1.06 (0.90-1.24)	53/4410	1695	1 [Reference]
100 to <110	386/9981	2984	1.41 (1.24-1.61)	1948/80 457	2349	1.21 (1.03-1.42)	430/22 314	2266	1.38 (1.04-1.85)
≥110	20/388	NC	NC	514/15 372	3060	1.50 (1.25-1.81)	893/32 485	3177	1.69 (1.26-2.26)
P for trend			<.001			<.001			<.001
Per 10-cm increase, continuous			1.16 (1.09-1.23)			1.18 (1.12-1.24)			1.21 (1.13-1.30)
Women									
<75	761/95 032	879	1 [Reference]	39/4808	NC	NC	3/283	NC	NC
75 to <85	1111/108 146	988	1.24 (1.12-1.37)	254/38 685	772	1 [Reference]	17/2145	NC	NC
85 to <95	608/42 144	1208	1.52 (1.34-1.73)	746/76 183	992	1.21 (1.04-1.40)	132/14 110	1070	1 [Reference]
95 to <105	144/6410	1762	2.04 (1.68-2.49)	514/37 950	1216	1.40 (1.19-1.65)	296/29 022	1153	0.94 (0.76-1.16)
≥105	19/504	NC	NC	173/8319	1642	1.77 (1.43-2.19)	515/30 198	1808	1.27 (1.03-1.57)
P for trend			<.001			<.001			<.001
Per 10-cm increase, continuous			1.25 (1.18-1.32)			1.15 (1.08-1.22)			1.13 (1.06-1.20)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; NC, not calculated (owing to <50 deaths in this category); RR, relative risk.

[a] Mortality rate per 100 000 person-years, standardized to the age distribution of men or women in the cohort.

[b] Adjusted for age, race, educational level, marital status, smoking status, alcohol use, height, physical activity, and BMI. Models for women were also adjusted for hormone therapy.

action). In addition, among men but not among women, RRs associated with WC appeared higher in the less physically active (*P*=.04 for interaction). Among men, RRs associated with a WC of 110 cm or more compared with less than 90 cm were 1.93 (95% CI, 1.59-2.35) in those with less than 7 metabolic equivalents per week and 1.58 (95% CI, 1.38-1.81) in those with 7 or more metabolic equivalents per week (data appear in text only).

Excluding the first 4 years of follow-up did not meaningfully change results in men or women. After exclusion of the first 4 years of follow-up, the BMI-adjusted RR among men was 1.88 (95% CI, 1.51-2.31) for WC of 120 cm or more compared with less than 90 cm. Among women, the BMI-adjusted RR was 2.46 (95% CI, 1.99-3.04) for WC of 110 cm or more compared with less than 75 cm.

Results by cause of death are given in **Table 5**. The WC was associated with increased risk of mortality within each category of cause of death we examined. However, the strength of the association was strongest for respiratory disease and all other causes, followed by cardiovascular disease and then cancer.

COMMENT

In this large prospective cohort, increased WC was associated with higher risk of mortality independent of BMI. After adjustment for BMI, increasing levels of WC were associated with progressively higher risk of mortality in men and women. The WC was also associated with higher risk of mortality within all categories of BMI in men and women. However, among women, the association between WC and mortality was strongest in those with a normal BMI.

Adjustment for BMI increased the strength of the association between WC and mortality in our study, as it did in most previous studies.[16,17,20,21,23] This may be explained by the fact that low WC was associated with low BMI, and low BMI was associated with increased mortality. Particularly in elderly people, a low BMI may reflect low lean body mass or the presence of diseases that can result in weight loss.[37,38] Adjustment of WC for BMI may have indirectly adjusted for low lean body mass and/or prevalent disease and therefore resulted in a less confounded estimate of the association between WC and mortality.

Our results are generally consistent with those of previous studies that have examined WC adjusted for BMI. All 6 of these previous studies[16,17,20-23] found a statistically significant positive association between WC and mortality. Results from the 2 smallest of these studies are difficult to compare with ours because the results were reported in terms of a percentage change[16] or a standard deviation change[17] in WC. The remaining 4 studies[20-23] examined risk by quintile of WC, with the highest quintile defined by a minimum WC ranging from 102 to 106 cm in men and from 87 to 96 cm in women. In these studies, RRs associated with the highest quintile of WC ranged from 1.2 to 2.0. We examined higher levels of WC (≥120 cm in men and ≥110 cm in women) than did the studies that examined quintiles, and we observed correspondingly higher RRs (RR=2.0 in men and 2.4 in women). To our knowledge, previous studies have not presented results for similarly high levels of WC, with the exception of graphical presentations based on spline models.[21,23]

In our study, WC was positively associated with risk of mortality among individuals within all categories of BMI examined (normal, overweight, and obese). The RRs associated with a 10-cm increase in WC ranged from approximately 15% to 25% within various categories of BMI, with the strongest association observed among women

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Table 4. All-Cause Mortality by Waist Circumference, Stratified by Prevalent Disease and Age, Cancer Prevention Study II Nutrition Cohort, 1997-2006

	Waist Circumference, cm										
	Men					Women					
Measure	<90	90 to <100	100 to <110	≥110	*P* Value[a]	<75	75 to <85	85 to <95	95 to <105	≥105	*P* Value[a]
Prevalent cancer, CVD, or respiratory disease at baseline											
No											
Deaths	584	1337	1001	498		376	704	723	441	294	
Multivariate RR (95% CI)[b]	1 [Reference]	0.92 (0.83-1.01)	1.03 (0.93-1.15)	1.24 (1.10-1.41)		1 [Reference]	1.15 (1.02-1.31)	1.26 (1.11-1.43)	1.36 (1.18-1.57)	1.77 (1.51-2.07)	
Multivariate- + BMI-adjusted RR (95% CI)[c]	1 [Reference]	1.03 (0.92-1.15)	1.16 (1.01-1.34)	1.30 (1.08-1.56)		1 [Reference]	1.37 (1.19-1.57)	1.70 (1.45-2.00)	1.91 (1.58-2.31)	2.31 (1.83-2.91)	
Yes											
Deaths	885	2318	1763	929		427	678	763	513	413	
Multivariate RR (95% CI)[b]	1 [Reference]	0.97 (0.90-1.05)	1.02 (0.94-1.11)	1.25 (1.14-1.38)	.61	1 [Reference]	0.87 (0.77-0.98)	0.90 (0.80-1.01)	0.96 (0.84-1.10)	1.27 (1.10-1.46)	.004
Multivariate- + BMI-adjusted RR (95% CI)[c]	1 [Reference]	1.16 (1.06-1.26)	1.35 (1.22-1.51)	1.71 (1.49-1.97)	.60	1 [Reference]	1.04 (0.91-1.19)	1.22 (1.05-1.42)	1.39 (1.16-1.66)	1.78 (1.44-2.19)	.004
Age at baseline											
<70 y											
Deaths	464	1038	842	508		360	573	560	336	312	
Multivariate RR (95% CI)[b]	1 [Reference]	0.89 (0.80-0.99)	1.04 (0.93-1.17)	1.24 (1.08-1.41)		1 [Reference]	1.04 (0.91-1.19)	1.10 (0.96-1.26)	1.12 (0.97-1.31)	1.75 (1.50-2.05)	
Multivariate- + BMI-adjusted RR (95% CI)[c]	1 [Reference]	0.98 (0.86-1.11)	1.15 (0.98-1.34)	1.24 (1.02-1.51)		1 [Reference]	1.27 (1.10-1.48)	1.53 (1.28-1.82)	1.61 (1.30-2.00)	2.24 (1.75-2.88)	
≥70 y											
Deaths	1005	2617	1922	919		443	809	926	618	395	
Multivariate RR (95% CI)[b]	1 [Reference]	0.99 (0.92-1.07)	1.05 (0.97-1.13)	1.30 (1.18-1.43)	.18	1 [Reference]	0.98 (0.87-1.10)	1.06 (0.95-1.19)	1.19 (1.05-1.35)	1.43 (1.24-1.65)	.12
Multivariate- + BMI-adjusted RR (95% CI)[c]	1 [Reference]	1.20 (1.10-1.30)	1.43 (1.29-1.58)	1.87 (1.64-2.14)	.003	1 [Reference]	1.16 (1.02-1.32)	1.46 (1.26-1.68)	1.75 (1.48-2.06)	2.10 (1.72-2.56)	.44

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; CVD, cardiovascular disease; RR, relative risk.

[a] *P* value for interaction.

[b] Adjusted for age, race, educational level, marital status, smoking status, alcohol use, height, and physical activity. Models for women were also adjusted for hormone therapy.

[c] Additionally adjusted for BMI.

in the normal BMI category. Our results are generally consistent with those from the few previous studies that have examined WC within categories of BMI. In the large National Institutes of Health—American Association of Retired Persons (NIH-AARP) cohort,[22] individuals in the normal BMI category who were abdominally obese (≥88 cm in women and ≥102 cm in men) were at approximately 20% higher risk than individuals with normal BMI who were not. Increasing quintiles of WC were associated with increasing risk within tertiles of BMI in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort,[23] as well as increased risk both higher and lower than a BMI cut point of 25.0 in the Nurses' Health Study.[21] To our knowledge, our study is the first to specifically examine the association between WC and mortality within each of the 3 standard categories of BMI (normal, overweight, and obese). Our results, together with those of previous studies, provide evidence that a larger WC may have important adverse health effects even among individuals with a BMI lower than 30, the threshold for being categorized as obese.

The higher risk of mortality associated with higher WC among individuals within the normal and overweight BMI categories documented in this study and others may affect the development of future clinical guidelines for obesity. Currently available clinical guidelines from the NIH are based on evidence from the 1990s.[25] These guidelines recommend that WC be used to identify increased disease risk only among individuals in the overweight and obese categories of BMI. In addition, the NIH guidelines recommend weight loss goals for all patients in the obese category of BMI (≥30), but they do not specifically recommend weight loss goals for abdominally obese patients (WC ≥88 cm in women or ≥102 cm in men) who are in the normal or overweight BMI category unless they also have 2 or more cardiovascular risk factors or a desire to lose weight.

We observed a somewhat stronger association between WC and mortality among women in the normal BMI category (18.5 to <25) than among women in the overweight or obese category of BMI. However, the association between WC and mortality did not differ by BMI among men. In the EPIC study, the association between WC and mortality appeared stronger in lower categories of BMI among men and women,[23] whereas in the Nurses' Health Study, which included only women,

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Table 5. Cause-Specific Mortality by Waist Circumference, Cancer Prevention Study II Nutrition Cohort, 1997-2006

	Waist Circumference, cm								
	Men				Women				
Measure	<90	90 to <100	100 to <110	≥110	<75	75 to <85	85 to <95	95 to <105	≥105
Cancer									
Deaths	474	1252	985	428	368	621	635	388	259
Multivariate RR (95% CI)[a]	1 [Reference]	1.02 (0.92-1.14)	1.16 (1.03-1.30)	1.18 (1.03-1.35)	1 [Reference]	1.02 (0.90-1.16)	1.07 (0.94-1.22)	1.12 (0.97-1.30)	1.35 (1.14-1.59)
Multivariate- + BMI-adjusted RR (95% CI)[b]	1 [Reference]	1.13 (1.00-1.27)	1.31 (1.13-1.52)	1.32 (1.09-1.60)	1 [Reference]	1.12 (0.97-1.30)	1.27 (1.07-1.50)	1.38 (1.13-1.69)	1.66 (1.31-2.12)
Cardiovascular									
Deaths	543	1338	1016	555	199	378	422	269	222
Multivariate RR (95% CI)[a]	1 [Reference]	0.96 (0.87-1.06)	1.07 (0.96-1.19)	1.41 (1.25-1.60)	1 [Reference]	1.07 (0.91-1.28)	1.18 (1.00-1.41)	1.29 (1.07-1.55)	1.95 (1.60-2.38)
Multivariate- + BMI-adjusted RR (95% CI)[b]	1 [Reference]	1.05 (0.93-1.17)	1.20 (1.04-1.38)	1.48 (1.24-1.77)	1 [Reference]	1.29 (1.06-1.55)	1.57 (1.27-1.95)	1.74 (1.35-2.23)	2.31 (1.72-3.10)
Respiratory									
Deaths	133	295	228	128	67	97	103	83	55
Multivariate RR (95% CI)[a]	1 [Reference]	0.80 (0.65-0.98)	0.82 (0.66-1.02)	1.06 (0.82-1.37)	1 [Reference]	0.80 (0.58-1.09)	0.80 (0.58-1.09)	1.06 (0.76-1.47)	1.19 (0.82-1.73)
Multivariate- + BMI-adjusted RR (95% CI)[b]	1 [Reference]	1.40 (1.10-1.78)	2.19 (1.63-2.93)	3.90 (2.69-5.66)	1 [Reference]	1.27 (0.90-1.78)	1.91 (1.29-2.83)	3.23 (2.04-5.12)	3.79 (2.17-6.62)
All other causes									
Deaths	319	770	535	316	169	286	326	214	171
Multivariate RR (95% CI)[a]	1 [Reference]	0.93 (0.81-1.06)	0.94 (0.81-1.09)	1.33 (1.13-1.56)	1 [Reference]	0.98 (0.81-1.18)	1.10 (0.92-1.33)	1.18 (0.96-1.46)	1.72 (1.38-2.14)
Multivariate- + BMI-adjusted RR (95% CI)[b]	1 [Reference]	1.16 (1.00-1.35)	1.36 (1.13-1.64)	2.01 (1.59-2.56)	1 [Reference]	1.25 (1.01-1.54)	1.73 (1.36-2.19)	2.03 (1.54-2.69)	2.75 (1.98-3.83)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; RR, relative risk.
[a] Adjusted for age, race, educational level, marital status, smoking status, alcohol use, height, and physical activity. Models for women were also adjusted for hormone therapy.
[b] Additionally adjusted for BMI.

the association between WC and mortality did not differ by BMI.[21] The reason for the stronger association between WC and mortality among women with low BMI in our study is unclear. Future detailed analyses of the relationship between WC and visceral adipose tissue or measures of insulin resistance within categories of BMI could identify biological reasons for potential differences in the strength of the association between WC and mortality.

In our study, associations with WC were strongest for mortality caused by respiratory disease, followed by cardiovascular disease and then cancer. This pattern of results is very similar to that seen in the EPIC cohort,[23] the largest previous study of WC and mortality to examine results by cause of death. In both our study and the EPIC cohort, WC adjusted for BMI was associated with a notable increase in respiratory disease mortality. However, WC was not associated with increased respiratory disease mortality in an earlier study that did not adjust for BMI.[18] The increased risk of respiratory disease mortality observed in our study and the EPIC study is consistent with the fact that a high WC is associated with considerably reduced respiratory function.[39,40]

The RRs associated with WC were statistically significantly lower among women with a history of diseases that could result in weight loss (cancer, cardiovascular disease, or respiratory disease) than among women without any of these illnesses. The reason for this difference is unclear. No similar difference was observed among men. Although our analysis excluded people with a weight loss of 10 lbs or more (≥4.5 kg) in the previous 5 years, it is possible that the association between WC and mortality among women with these diseases was still attenuated by disease-related weight loss. Alternatively, women who had a history of these diseases had considerably higher mortality rates than women who did not. Therefore, similar increases in absolute risk associated with WC would be expected to result in smaller increases in RR among women with these diseases than among those without them.

Although WC was associated with increased risk among men in our study regardless of age, RRs associated with WC (after adjustment for BMI) were statistically significantly lower in men younger than 70 years than in those 70 years or older. The RRs did not differ by age among women. Our results by age among men contrast with those of studies of BMI and mortality, in which RRs are often lower among elderly people.[41] The reason for the lower RRs associated with WC among men younger than 70 years in our study is unclear, although it may have been due partly to chance. All men in the EPIC analysis were 70 years or younger, but RRs associated with WC in EPIC were substantially higher than those among comparably aged men in our study.[23] Alternatively, the lower RRs associated with WC among the younger men in our study may have been due to a weaker association between WC and the amount of vis-

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ceral adipose tissue among younger compared with older men,[42] although all the men in our study were 50 years or older.

This study has several strengths. First, we report results for very high levels of WC that, to our knowledge, have not been examined in previous studies of mortality. Second, we used WC categories based on 5- or 10-cm increments rather than quintiles of our study population, making results more easily applicable to other populations. Third, we excluded participants who reported losing 10 lbs or more (≥4.5 kg) in the previous 5 years, reducing the potential for bias due to disease-related weight loss. Finally, this analysis included nearly 15 000 deaths, considerably more than previous studies with the exception of the similar-sized EPIC cohort[23] and the somewhat larger NIH-AARP cohort (approximately 25 000 deaths).[22] The large size of our study allowed us to examine WC within 3 standard clinical categories of BMI (normal, overweight, and obese).

Limitations of this study include the fact that study participants measured and reported their own WC, undoubtedly introducing some measurement error. However, self-measured WC was documented to be reasonably accurate in other study populations.[28,29] In addition, because this is an observational study, the association between WC and mortality might be overestimated because of confounding by factors associated with both larger WC and higher mortality. Finally, all study participants were 50 years or older, and nearly all were white. Results may not be generalizable to younger populations or those of other racial or ethnic backgrounds, although similar results have been observed in the considerably younger EPIC cohort (mean age, 51 years)[23] and in a Chinese cohort.[20]

Results from this large prospective study emphasize the importance of WC as a risk factor for mortality in older adults, regardless of whether the BMI is categorized as normal, overweight, or obese. Our results suggest that, regardless of weight, avoiding gains in WC may reduce risk of premature mortality.

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