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Abdominal Obesity and the Risk of All-Cause, Cardiovascular, and Cancer Mortality
Sixteen Years of Follow-Up in US Women

Cuilin Zhang, MD, PhD; Kathryn M. Rexrode, MD, MPH; Rob M. van Dam, PhD; Tricia Y. Li, MD, MS; Frank B. Hu, MD, PhD

***Background*—**Accumulating evidence indicates that abdominal adiposity is positively related to cardiovascular disease (CVD) risk and some other diseases independently of overall adiposity. However, the association of premature death resulting from these diseases with abdominal adiposity has not been widely studied, and findings are inconsistent.

***Methods and Results*—**In a prospective cohort study of 44 636 women in the Nurses' Health Study, associations of abdominal adiposity with all-cause and cause-specific mortality were examined. During 16 years of follow-up, 3507 deaths were identified, including 751 cardiovascular deaths and 1748 cancer deaths. After adjustment for body mass index and potential confounders, the relative risks across the lowest to the highest waist circumference quintiles were 1.00, 1.11, 1.17, 1.31, and 1.79 (95% confidence interval [CI], 1.47 to 1.98) for all-cause mortality; 1.00, 1.04, 1.04, 1.28, and 1.99 (95% CI, 1.44 to 2.73) for CVD mortality; and 1.00, 1.18, 1.20, 1.34, and 1.63 (95% CI, 1.32 to 2.01) for cancer mortality (all $P<0.001$ for trend). Among normal-weight women (body mass index, 18.5 to <25 kg/m^2), abdominal obesity was significantly associated with elevated CVD mortality: Relative risk associated with waist circumference $\geq$88 cm was 3.02 (95% CI, 1.31 to 6.99) and for waist-to-hip ratio $>$0.88 was 3.45 (95% CI, 2.02 to 6.92). After adjustment for waist circumference, hip circumference was significantly and inversely associated with CVD mortality.

***Conclusions*—**Anthropometric measures of abdominal adiposity were strongly and positively associated with all-cause, CVD, and cancer mortality independently of body mass index. Elevated waist circumference was associated with significantly increased CVD mortality even among normal-weight women. **(*Circulation*. 2008;117:1658-1667.)**

Key Words: adiposity ■ cancer ■ cardiovascular diseases ■ mortality ■ obesity ■ waist-hip ratio

In parallel with the increase in overall body adiposity in the US population, the prevalence of abdominal obesity increased substantially during the past 15 years.[1] More than half of US adults had abdominal obesity in the period of 2003 to 2004.[1] Growing evidence suggests that abdominal obesity is particularly detrimental.[2] Greater abdominal adiposity is strongly associated with insulin resistance, dyslipidemia, and systematic inflammation, which play essential roles in the pathogenesis of cardiovascular disease (CVD), metabolic syndrome, and certain cancers.[2,3]

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Waist circumference (WC) and waist-to-hip ratio (WHR) are widely used as indirect measures of abdominal or central adiposity in epidemiological studies. Although the definition of abdominal obesity remains in dispute, the cutoffs for WC (102 cm for men, 88 cm for women) and WHR (0.95 for men, 0.88 for women) were recommended by the American Heart Association and the US Department of Agriculture. Recently, waist-to-height ratio was suggested as an alternative to WHR because it provides a correction for body frame size using height, which is more conveniently measured than hip circumference.[4–6] Accumulating evidence indicated that the above measures of abdominal adiposity were significantly and positively associated with risks for chronic diseases such as CVD, diabetes mellitus, and some cancers independently of overall adiposity.[7] The association of these measures with mortality, however, has not been widely studied, and findings have been controversial.[8–12] The inconsistencies of findings

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From the Epidemiology Branch, Division of Epidemiology, Statistics, and Prevention Research, National Institute of Child Health and Human Development, Bethesda, Md (C.Z.); Division of Preventive Medicine (K.M.R.) and Channing Laboratory (R.M.v.D., F.B.H.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass; and Departments of Nutrition (R.M.v.D., T.Y.L., F.B.H.) and Epidemiology (F.B.H.), Harvard School of Public Health, Boston, Mass.
Guest Editor for this article was Robert Eckel, MD.
Reprint requests to Cuilin Zhang, MD, PhD, Epidemiology Branch, Division of Epidemiology, Statistics, and Prevention Research, National Institute of Child Health and Human Development, 6100 Executive Blvd, Room 7B03, MSC 7510, 9000 Rockville Pike, Bethesda, MD 20892–7510. E-mail zhangcu@mail.nih.gov or nhbfh@channing.harvard.edu

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Table 1. Age-Adjusted Characteristics According to Baseline (1986) Measures of Abdominal Adiposity

	WC Quintiles			WHR Quintiles			Waist-to-Height Ratio Quintiles		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Range, in	<28	30–31	≥35	<0.73	0.76–0.79	≥0.84	<0.42	0.46–0.48	≥0.53
Women, n	9662	8224	7705	8799	8815	9063	8884	8921	9030
Age, y*	50.4 (7.0)	53.1 (7.0)	54.3† (6.9)	50.4 (6.9)	52.6 (7.1)	54.7† (6.9)	50.1 (6.9)	53.0 (6.9)	54.4† (6.9)
BMI, kg/m²	20.9 (0.03)	23.9 (0.03)	30.9† (0.03)	22.6 (0.04)	24.1 (0.04)	27.4† (0.04)	20.6 (0.03)	23.7 (0.03)	30.4† (0.03)
Physical activity, h/wk	2.9 (0.04)	2.0 (0.04)	1.2† (0.04)	2.7 (0.04)	2.1 (0.04)	1.5† (0.04)	2.9 (0.04)	2.1 (0.04)	1.3† (0.04)
Alcohol, g/d	6.6 (0.11)	6.9 (0.12)	4.9 (0.12)	5.7 (0.11)	6.6 (0.11)	6.6 (0.12)	6.8 (0.12)	6.8 (0.11)	4.9 (0.11)
Never smokers, %	21.6	18.3	17.6	21.8	19.5	18.7	19.6	19.6	21.1
Postmenopausal hormone use, %	40.4	37.7	26.7†	40.8	36.5	27.5†	40.9	36.4	26.3†
Hypertension, %	13.1	19.3	39.3†	13.5	20.3	33.9†	12.9	19.1	38.0†
Hypercholesterolemia, %	8.5	10.6	16.7†	8.6	10.7	16.9†	7.9	11.0	16.9†
Family history of MI	19.4	19.3	21.5	19.1	19.4	21.6	18.9	19.8	21.2
WC, in	26.0 (0.02)	30.4 (0.02)	38.1† (0.02)	27.1 (0.03)	30.3 (0.03)	35.5† (0.03)	26.2 (0.02)	30.1 (0.02)	37.3† (0.02)
WHR	0.72 (0.0006)	0.78 (0.0006)	0.86† (0.0006)	0.70 (0.0004)	0.77 (0.0004)	0.88† (0.0004)	0.72 (0.0006)	0.78 (0.0006)	0.85† (0.0006)
Waist-to-height ratio	0.41 (0.0003)	0.47 (0.0003)	0.59† (0.0003)	0.42 (0.0005)	0.47 (0.0005)	0.55† (0.0005)	0.40 (0.0003)	0.47 (0.0003)	0.58† (0.0003)
Height, in	63.8 (0.02)	64.7 (0.03)	64.9† (0.03)	64.4 (0.03)	64.5 (0.03)	64.5 (0.03)	65.0 (0.02)	64.4 (0.02)	64.1† (0.02)
Hip circumference, in	36.2 (0.03)	39.2 (0.03)	44.7† (0.03)	38.9 (0.04)	39.3 (0.04)	40.3 (0.04)	36.5 (0.03)	38.9 (0.03)	43.9† (0.03)

Q1 is the lowest quintile; Q3, the medium quintile; and Q5, the highest quintile. All data are presented as mean (SD) unless otherwise specified.
*Unadjusted mean (SD).
†Test for linear trend across quintiles of measures of abdominal adiposity were statistically significant ($P<0.05$).

can be due to differences in study populations and sampling (eg, age, gender, distribution of lifestyle factors related to adiposity such as smoking status, inclusion of individuals with chronic diseases related to adiposity, and duration of follow-up), measures of abdominal adiposity, and analytic approaches. Furthermore, few studies have investigated the joint and independent effects of abdominal and overall adiposity. With the consideration of major factors contributing to the heterogeneity of previous findings, we investigated several measures of abdominal adiposity—WC, WHR, and waist-to-height ratio—in relation to all-cause, CVD, and cancer mortality during the 16 years of follow-up of the Nurses' Health Study.

Methods

Population

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses 30 to 55 years of age who resided in 11 large US states completed a mailed questionnaire on their medical history and lifestyle. The cohort continues to be followed up every 2 years by questionnaire to update information on potential risk factors and to identify cases of newly diagnosed diseases (ie, CVD, diabetes mellitus, and cancers). We restricted our analysis to those 44 636 women who reported WC in the 1986 questionnaire who also were free of a prior history of CVD and cancer. Age, body weight, and major social demographic and clinical characteristics of those who reported WC were not appreciably different from those who did not report it.

Table 2. Correlations* of WC, WHR, Waist-to Height Ratio, Hip Circumference, Height, and BMI

	WC	HR	Waist-to-Height Ratio	Hip Circumference
WC, in	1.00	. . .	. . .	. . .
WHR	0.65	1.00	. . .	. . .
Waist-to-height ratio	0.96	0.65	1.00	. . .
Hip circumference, in	0.77	0.02	0.71	1.00
Height, in	0.14	−0.0098	−0.13	0.20
BMI, kg/m²	0.81	0.33	0.83	0.81

*$P<0.0001$ except for the correlation between WHR and height ($P=0.038$).

Assessment of Overall and Abdominal Adiposity

As a measure of overall adiposity, we calculated body mass index (BMI) as weight in kilograms divided by the square of height in meters (kg/m²). Self-reported weights were validated in a subsample of 184 Nurses' Health Study participants living in the Boston, Mass, area and were highly correlated with actual measured weights ($r=0.96$; [mean difference: self-reported weight−measured weight]=−1.5 kg [SD, 2.98 kg]).[13] In 1986, Nurses' Health Study participants measured and reported measurements of their waist (at the umbilicus) and hip circumference (the largest circumference) to the nearest quarter-inch. To validate these measurements, self-reported measures in a sample of 140 nurses were compared with 2 standardized measurements taken ≈6 months apart by technicians who visited participants in their homes. The distributions for age, BMI, and other sociodemographic characteristics of women in this sample are similar to those in the parent cohort. The correlations between self-reported and technician-measured circumferences were 0.89 for the waist (mean difference: [self-reported−measured]=−0.05 in [SD, 1.99 in]), 0.84 for the hip (mean difference: [self-reported−measured]=−0.54 in [SD, 2.01 in]), and 0.70 for the WHR (mean difference: [self-reported−measured]=−0.011 [SD, 0.049]).[14] In addition, no significant linear trends in correlations were present for WC across quartiles of BMI, and no effect modification was noted by age or BMI on the validity of self-reported circumference measures.

Ascertainment of Covariates

Every 2 years, we update participants' smoking status, menopausal status, and postmenopausal hormone use status. We also inquire about physician-diagnosed hypertension and high cholesterol. In a subsample, self-reports were compared with medical records and found to be highly accurate.[15] Alcohol consumption was assessed by a validated food frequency questionnaire that included questions about average daily consumption of beer, wine, and spirits during the

Table 3. Multivariable RRs of Mortality According to Quintiles of WC

	WC, in					Each SD Increase	*P* for Linear Trend
	<28	28–29	30–31	32–34	≥35		
Median, in	26.0	28.0	30.0	33.0	37.0	4.276	
Person-y	149 433	156 251	126 575	138 236	117 025		
All-cause mortality	565	682	608	776	876		
RR1 (age-adjusted)	1.0 (Ref)	1.01 (0.90–1.13)	1.02 (0.91–1.14)	1.10 (0.98–1.22)	1.48 (1.32–1.64)	1.18 (1.13–1.23)	<0.001
RR2*	1.0 (Ref)	1.01 (0.90–1.13)	1.02 (0.90–1.14)	1.09 (0.97–1.21)	1.44 (1.29–1.60)	1.18 (1.13–1.23)	<0.001
RR3† (model 2+BMI)	1.0 (Ref)	1.11 (0.99–1.25)	1.17 (1.04–1.32)	1.31 (1.16–1.48)	1.71 (1.47–1.98)	1.34 (1.23–1.39)	<0.001
Smoking stratification‡							
Never smokers	1.0 (Ref)	1.31 (1.05–1.64)	1.44 (1.14–1.81)	1.46 (1.15–1.87)	2.07 (1.57–2.72)	1.24 (1.13–1.34)	<0.001
Ever smokers	1.0 (Ref)	1.03 (0.90–1.18)	1.03 (0.90–1.19)	1.25 (1.08–1.45)	1.59 (1.33–1.90)	1.34 (1.23–1.45)	<0.001
Age stratification, y‡							
≤55	1.0 (Ref)	1.05 (0.88–1.26)	1.13 (0.93–1.37)	1.21 (0.98–1.51)	1.45 (1.10–1.89)	1.13 (1.04–1.23)	0.002
>55	1.0 (Ref)	1.11 (0.95–1.28)	1.12 (0.95–1.30)	1.22 (1.04–1.42)	1.59 (1.32–1.90)	1.28 (1.18–1.34)	<0.001
Menopause stratification‡							
Premenopausal	1.0 (Ref)	1.12 (0.87–1.45)	1.27 (0.96–1.67)	1.39 (1.02–1.90)	1.64 (1.11–2.41)	1.18 (1.04–1.34)	0.008
Postmenopausal	1.0 (Ref)	1.12 (0.98–1.27)	1.14 (0.99–1.30)	1.30 (1.13–1.49)	1.71 (1.46–2.01)	1.28 (1.23–1.34)	<0.001
BMI stratification, kg/m^2‡							
<25	1.0 (Ref)	1.23 (1.11–1.41)	1.48 (1.29–1.70)	1.89 (1.61–2.21)	2.35 (1.82–3.05)	1.39 (1.34–1.50)	<0.001
≥25	1.0 (Ref)	1.39 (0.66–2.94)	1.30 (0.64–2.65)	1.40 (0.69–2.81)	1.78 (0.88–3.58)	1.34 (1.23–1.45)	<0.001
CVD mortality	109	127	107	161	247		
RR1 (age-adjusted)	1.0 (Ref)	0.94 (0.73–1.21)	0.89 (0.69–1.17)	1.11 (0.87–1.42)	2.02 (1.61–2.54)	1.39 (1.34–1.50)	<0.001
RR2*	1.0 (Ref)	0.94 (0.73–1.22)	0.91(0.69–1.18)	1.09 (0.65–1.40)	1.92 (1.52–2.49)	1.39 (1.28–1.45)	<0.001
RR3† (model 2+BMI)	1.0 (Ref)	1.04 (0.80–1.36)	1.04 (0.78–1.36)	1.28 (0.97–1.69)	1.99 (1.44–2.73)	1.45 (1.28–1.56)	<0.001
Cancer mortality	268	358	311	401	410		
RR1 (age-adjusted)	1.0 (Ref)	1.14 (0.97–1.33)	1.12 (0.95–1.32)	1.25 (1.07–1.46)	1.51 (1.29–1.76)	1.13 (1.09–1.18)	<0.001
RR2*	1.0 (Ref)	1.14 (0.98–1.34)	1.14 (0.97–1.34)	1.25 (1.07–1.46)	1.53 (1.31–1.79)	1.18 (1.09–1.23)	<0.001
RR3† (model 2+BMI)	1.0 (Ref)	1.18 (1.01–1.39)	1.20 (1.01–1.42)	1.34 (1.13–1.61)	1.63 (1.32–2.01)	1.18 (1.13–1.28)	<0.001
Mortality of obesity-related cancer§	186	248	204	253	270		
RR1 (age-adjusted)	1.0 (Ref)	1.14 (0.94–1.38)	1.07 (0.88–1.31)	1.14 (0.94–1.38)	1.44 (1.19–1.74)	1.13 (1.04–1.18)	<0.001
RR2*	1.0 (Ref)	1.15 (0.95–1.40)	1.10 (0.90–1.34)	1.17 (0.96–1.41)	1.51 (1.24–1.83)	1.13 (1.09–1.23)	<0.001
RR3† (model 2+BMI)	1.0 (Ref)	1.21 (1.00–1.47)	1.18 (0.96–1.45)	1.30 (1.05–1.62)	1.70 (1.31–2.20)	1.18 (1.09–1.28)	<0.001

Ref indicates reference. Values in parentheses are 95% CIs.

*Model 2 was adjusted for age (5-year interval), quintiles of physical activity, alcohol consumption (0, 0.1 to 4.9, 5.0 to 14.9, ≥15.0 g/d), family history of MI, smoking status (never, past, current [1 to 14, 15 to 24, 25+ cigarettes a day]), and menopausal status and hormone use (premenopausal status, postmenopausal status, and hormone never use, past use, and current use).

†Model 3 was adjusted for variables in model 2 and BMI (<18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, and ≥35 kg/m^2).

‡RRs in stratified analyses were adjusted for factors in model 3 except the stratified factor.

§Cancers thought to be linked with adiposity (colon cancer, breast cancer, pancreatic cancer, uterine, ovarian, and kidney cancer).

previous year.[16] We asked women about the average time spent per week on the following physical activities: walking, jogging, running, bicycling, lap swimming, playing tennis or squash, and calisthenics.[17] In a validation study, the correlation between physical activity reported on the 1-week recalls and that reported on the questionnaire was 0.79.[18] The correlation between moderate to vigorous activity reported in diaries and that reported on questionnaire was 0.62.

End Points

Deaths were reported by next of kin and the postal system or ascertained through the National Death Index. Follow-up for deaths was >98% complete.[19] For all deaths, we sought death certificates and, when appropriate, requested permission from the next of kin to review medical records (subject to state regulations). Underlying cause of death was assigned according to the *International Classification of Diseases*, eighth revision (ICD-8). Deaths were divided into those resulting from CVD (ICD-8 codes 390.0 to 458.9 and 795.0 to 795.9), cancer (ICD-8 codes 140.0 to 207.9), and other causes.

Statistical Analysis

We grouped women into quintile categories of WC, WHR, waist-to-height ratio, or hip circumference at baseline (1986). Participants contributed person-time from the date of return of the 1986 questionnaires until the date of death or June 1, 2002, whichever came first. The relative risk (RR) was calculated as the rate for a given category of the above measurements compared with the lowest category. Age-adjusted analyses were conducted with 5-year age categories using the Mantel-Haenszel method.[20] Cox proportional-hazards regression[21] was used to adjust for age and other potential confounders at baseline, including smoking, alcohol use, menopausal status/postmenopausal hormone use, physical activity, and parental

Table 4. Multivariable RRs of Mortality According to Quintiles of WHR

	WHR					Each SD Increase	*P* for Linear Trend
	<0.73	0.73–0.75	0.76–0.79	0.80–0.83	≥0.84		
Median	0.703	0.743	0.771	0.806	0.865	0.074	. . .
Person-y	136 679	140 351	135 961	137 293	137 236	. . .	. . .
All-cause mortality	433	562	619	802	1091	. . .	. . .
RR1 (age-adjusted)	1.0 (Ref)	1.13 (0.99–1.28)	1.21 (1.07–1.37)	1.44 (1.28–1.62)	1.85 (1.65–2.07)	1.17 (1.15–1.20)	<0.001
RR2*	1.0 (Ref)	1.08 (0.95–1.22)	1.12 (0.99–1.27)	1.31 (1.16–1.47)	1.58 (1.41–1.77)	1.14 (1.11–1.17)	<0.001
RR3† (model 2+BMI)	1.0 (Ref)	1.09 (0.96–1.23)	1.14 (1.00–1.29)	1.33 (1.18–1.50)	1.59 (1.41–1.79)	1.13 (1.10–1.16)	<0.001
Smoking stratification‡							
Never smokers	1.0 (Ref)	1.23 (0.99–1.53)	1.13 (0.91–1.41)	1.43 (1.16–1.76)	1.70 (1.37–2.09)	1.12 (1.06–1.17)	<0.001
Ever smokers	1.0 (Ref)	1.03 (0.88–1.20)	1.16 (1.00–1.35)	1.35 (1.16–1.56)	1.66 (1.44–1.91)	1.17 (1.13–1.21)	<0.001
Age stratification, y‡							
≤55	1.0 (Ref)	1.12 (0.93–1.36)	1.04 (0.85–1.27)	1.29 (1.06–1.56)	1.49 (1.22–1.82)	1.10 (1.04–1.16)	<0.001
>55	1.0 (Ref)	1.01 (0.86–1.20)	1.12 (0.95–1.32)	1.25 (1.07–1.46)	1.44 (1.24–1.68)	1.13 (1.09–1.17)	<0.001
Menopause stratification‡							
Premenopausal	1.0 (Ref)	1.36 (1.03–1.78)	1.33 (1.01–1.77)	1.47 (1.11–1.95)	1.71 (1.28–2.29)	1.12 (1.04–1.21)	<0.001
Postmenopausal	1.0 (Ref)	1.01 (0.88–1.17)	1.08 (0.94–1.24)	1.29 (1.13–1.47)	1.53 (1.34–1.74)	1.14 (1.11–1.17)	<0.001
BMI stratification, kg/m^2‡							
<25	1.0 (Ref)	1.15 (0.99–1.32)	1.23 (1.06–1.42)	1.51 (1.31–1.74)	1.80 (1.55–2.09)	1.17 (1.13–1.21)	<0.001
≥25	1.0 (Ref)	0.96 (0.73–1.27)	0.93 (0.72–1.20)	1.09 (0.86–1.39)	1.34 (1.07–1.69)	1.12 (1.07–1.16)	0.001
CVD mortality	90	112	114	149	286		
RR1 (age-adjusted)	1.0 (Ref)	1.04 (0.79–1.37)	1.03 (0.78–1.36)	1.21 (0.93–1.58)	2.17 (1.71–2.75)	1.23 (1.18–1.28)	<0.001
RR2*	1.0 (Ref)	1.00 (0.76–1.32)	0.95 (0.72–1.25)	1.10 (0.84–1.42)	1.82 (1.43–2.31)	1.20 (1.14–1.26)	<0.001
RR3† (model 2+BMI)	1.0 (Ref)	0.99 (0.75–1.31)	0.93 (0.71–1.23)	1.05 (0.81–1.38)	1.63 (1.27–2.09)	1.17 (1.11–1.23)	<0.001
Cancer mortality	220	300	336	422	470		
RR1 (age-adjusted)	1.0 (Ref)	1.20 (1.01–1.43)	1.32 (1.11–1.56)	1.54 (1.30–1.81)	1.62 (1.38–1.90)	1.12 (1.08–1.17)	<0.001
RR2*	1.0 (Ref)	1.15 (0.97–1.37)	1.23 (1.04–1.46)	1.42 (1.20–1.67)	1.43 (1.22–1.69)	1.10 (1.05–1.14)	<0.001
RR3† (model 2+BMI)	1.0 (Ref)	1.15 (0.96–1.37)	1.22 (1.03–1.45)	1.39 (1.18–1.64)	1.37 (1.16–1.62)	1.08 (1.03–1.13)	<0.001
Mortality of obesity-related cancer§	146	205	219	278	313		
RR1 (age-adjusted)	1.0 (Ref)	1.24 (1.00–1.52)	1.30 (1.05–1.60)	1.54 (1.26–1.88)	1.64 (1.34–2.00)	1.12 (1.07–1.18)	<0.001
RR2*	1.0 (Ref)	1.19 (0.96–1.47)	1.22 (0.99–1.50)	1.42 (1.16–1.74)	1.46 (1.19–1.78)	1.10 (1.04–1.15)	<0.001
RR3† (model 2+BMI)	1.0 (Ref)	1.19 (0.96–1.47)	1.22 (0.98–1.50)	1.41 (1.15–1.73)	1.42 (1.15–1.75)	1.09 (1.03–1.14)	0.004

Ref indicates reference. Values in parentheses are 95% CIs.

*Model 2 was adjusted for age (5-year interval), quintiles of physical activity, alcohol consumption (0, 0.1–4.9, 5.0–14.9, ≥15.0 g/d), family history of MI, smoking status (never, past, current [1–14, 15–24, 25+ cigarettes a day]), and menopausal status and hormone use (premenopausal status, postmenopausal status, and hormone never use, past use, and current use).

†Model 3 was adjusted for variables in model 2 and BMI (<18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, and ≥35 kg/m^2).

‡RRs in stratified analyses were adjusted for factors in model 3 except the stratified factor.

§Cancers thought to be linked with adiposity (colon cancer, breast cancer, pancreatic cancer, uterine, ovarian, and kidney cancer).

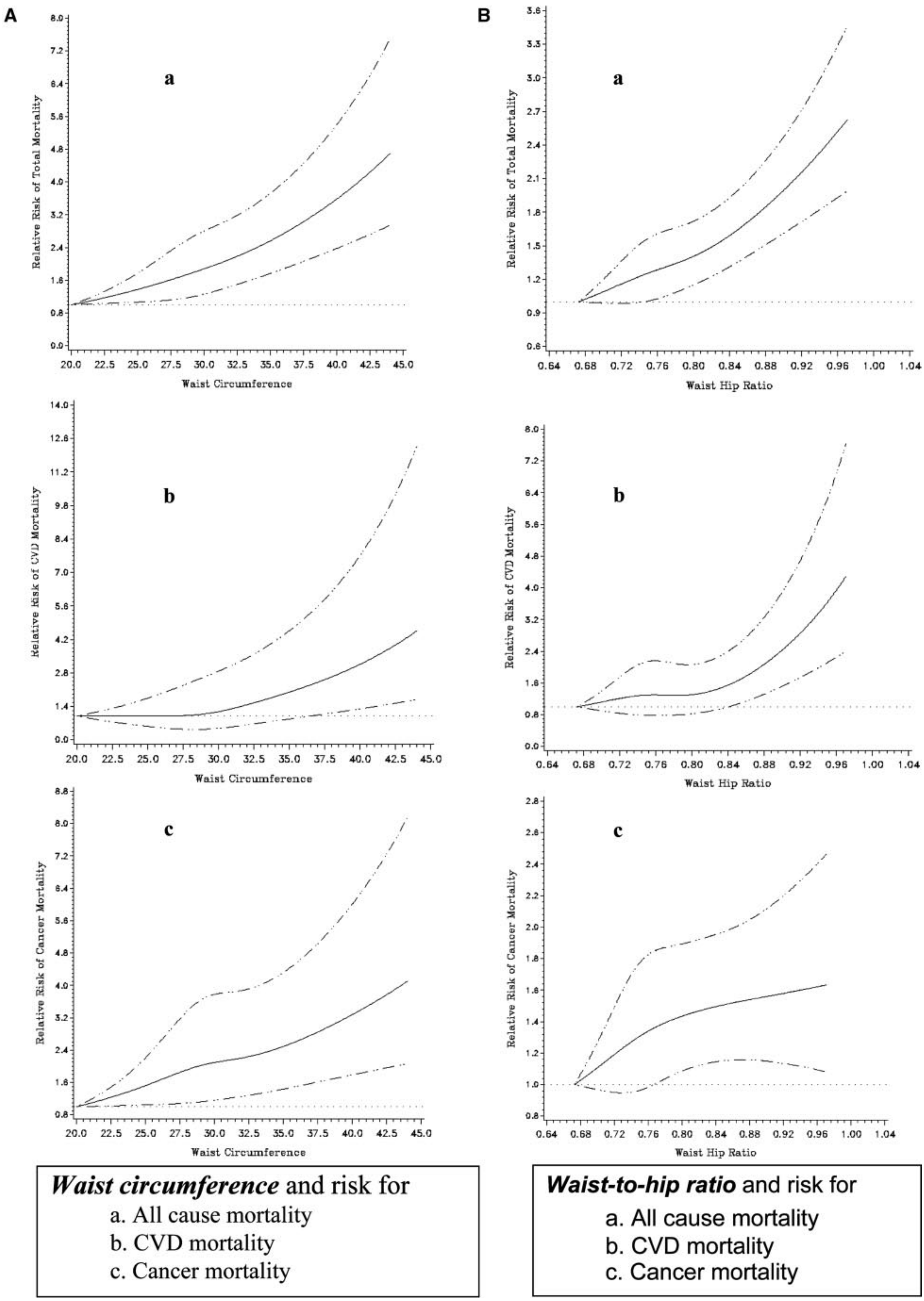
history of myocardial infarction (MI) <60 years of age. To examine whether the relationship between abdominal obesity and mortality was affected by overall adiposity, we further adjusted for BMI (<18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, ≥35 kg/m^2). In sensitivity analysis, we also fitted BMI as a continuous variable and included a nonlinear term of age (age^2) in Cox regression models. In addition, we used restricted cubic spline transformations with 4 knots to flexibly model the relation between measurements of abdominal adiposity (as continuous variables) and mortality, avoiding the need for prior specification of the risk function or the location of a threshold exposure value.[22]

We evaluated whether the association between abdominal adiposity and mortality was modified by major baseline characteristics such as age (≤55 years versus >55 years), smoking status (never versus ever), menopause status (premenopausal versus postmenopausal), and overall adiposity (BMI <25 versus ≥25 kg/m^2) in stratified analyses. Tests of trend were conducted using the median value for each category of measurements of abdominal adiposity as a continuous variable in multivariate models. Tests for interaction were performed with likelihood ratio tests by comparing 2 nested multivariate models with and without the interaction term. All statistical analyses were conducted with SAS version 8.2 (SAS Institute Inc, Cary, NC). All probability values were 2 sided.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

During 16 years of follow-up (687 519 person-years), we identified 3507 deaths, including 751 CVD deaths and 1748 cancer deaths. At baseline (1986), higher levels of WC,


A
B
a
b
c
Relative Risk of Total Mortality
Relative Risk of CVD Mortality
Relative Risk of Cancer Mortality
Waist Circumference
Waist Hip Ratio
Waist circumference and risk for
a. All cause mortality
b. CVD mortality
c. Cancer mortality
Waist-to-hip ratio and risk for
a. All cause mortality
b. CVD mortality
c. Cancer mortality

WHR, and waist-to-height ratio were associated with lower levels of physical activity and a lower likelihood of postmenopausal hormone use but with a greater likelihood of clinical hypertension and hypercholesterolemia (Table 1). The different anthropometric measures of abdominal obesity were highly correlated (Table 2). In addition, these measures were all significantly correlated with BMI, although the correlation for WHR (r=0.33) was not as strong as those with WC (r=0.81) and waist-to-height ratio (r=0.83).

After adjustment for age, smoking, and other covariates, both increasing WC and WHR were strongly associated with a graded increase in all-cause mortality (Tables 3 and 4). In general, the association for WC became stronger after adjustment for BMI. Similar results were observed in sensitivity analysis when BMI was fitted as continuous variable or when a nonlinear term of age (age^2) was added to regression models. Spline regression showed linear association of both WC and WHR with all-cause, CVD, and cancer mortality (Figure 1), and probability values for test for departure from linearity were not significant (P>0.05). In stratified analyses, the associations of WC and WHR with mortality were not appreciably different between never and ever smokers, between younger (≤55 years of age) and older (>55 years of age) women, and between premenopausal and postmenopausal women. Even among women who were neither overweight nor obese, both WC and WHR were strongly associated with mortality. Similar associations were observed between waist-to-height ratio and mortality. After adjustment for BMI and other covariates, RR and 95% confidence interval (CI) across the lowest to the highest quintile of waist-to-height ratio were 1.00, 1.09, 1.09, 1.22, and 1.54 (95% CI, 1.32 to 1.78) for all-cause mortality; 1.00, 0.81, 0.78, 1.20, and 1.52 (95% CI, 1.11 to 2.09) for CVD mortality; and 1.00, 1.33, 1.21, 1.28, and 1.56 (95% CI, 1.26 to 1.93) for cancer mortality (all P<0.001 for trend).

The association of hip circumference with CVD and cancer mortality was J shaped after adjustment for age, smoking status, physical activity, and other lifestyle and medical covariates so that the lowest mortality was observed among those in the third quintile (Table 5). After adjustment for WC, greater hip circumference was associated with lower all-cause and CVD mortality but not cancer mortality.

We next examined the joint effects of abdominal (WC and WHR) and overall (BMI) adiposity using the currently recommended cutoffs for BMI (≥25 or ≥30 kg/m^2), WC (≥35 in [88 cm]), and WHR (≥0.88) (Figure 2). Because smokers tend to weigh less but have much higher mortality rates than nonsmokers, which can lead to the artifact of an apparent elevation in risk of mortality among leaner individuals, we restricted the analyses to never smokers. In addition, because a very low BMI in some older adults may reflect ill health that we could not completely control for even after excluding prevalent cancer and heart disease, we excluded underweight women (BMI <18.5 kg/m^2). The highest mortality risk was observed among those who had both abdominal and overall obesity. However, even among normal-weight women, abdominal obesity was associated with significantly higher risk for CVD mortality: RR associated with larger WC ≥88 cm [35 in] was 3.02 (95% CI, 1.31 to 6.99) and for WHR >0.88 was 3.45 (95% CI, 2.02 to 6.92). In addition, within each category of WC or WHR, higher BMI was associated with increased total, CVD, and cancer mortality.

Discussion

In the present study of a large prospective cohort of US women, we observed a monotonic dose–response relationship between abdominal adiposity, as measured by WC, WHR, or waist-to-height ratio, and the risk of death among both younger (<55 years of age) and older (≥55 years of age) women and among both never and ever smokers. This positive association persisted in normal-weight women.

The prospective design and high rate of follow-up in this study minimized the possibility of recall bias or bias resulting from loss of follow-up. Furthermore, the large size of the study increased the precision of the RR estimates, and the extensive information on potential confounders allowed us to control for confounding in detail. One potential limitation is that the anthropometric measures of adiposity in the present study were by self-report. However, the validity of self-reported weight and waist and hip circumferences compared with technician measurements was high in this population of health professionals.[15,23] Because of the prospective design of this study, misclassification would be nondifferential and expected to bias the risk estimate toward the null. A major concern in analyzing the relationship between obesity and subsequent mortality is the problem of reverse causation (ie, weight loss can be the result, rather than the cause, of underlying illness).[24] To address this concern, we excluded participants with existing CVD and cancer at baseline.

Although a number of epidemiological studies have demonstrated that measures of abdominal adiposity significantly predict chronic diseases such as CVD and diabetes mellitus independently of overall body adiposity,[7] the associations of these measures with premature death have not been widely studied, and previous findings[8–12] have been inconsistent. The inconsistencies of findings may be related to differences in study populations and sampling, measures of abdominal adiposity, and analytic approaches. Our findings are in general consistent with those supporting an independent contribution of body fat distribution to mortality and the importance of abdominal adiposity in predicting mortality in women. In the Iowa Women's Health Study,[9] both WC and WHR were significantly associated with mortality, particularly coronary heart disease mortality. Likewise, in both a Danish cohort[10] and a Swedish cohort[12] of middle-aged and

Figure 1. RRs of all-cause, CVD, and cancer mortality according to WC (A) and WHR (B). RRs are adjusted for age (5-year interval), quintiles of physical activity, alcohol consumption (0, 0.1 to 4.9, 5.0 to 14.9, ≥15.0 g/d), family history of MI, smoking status (never, past, current [1 to 14, 15 to 24, 25+ cigarettes a day]), menopausal status and hormone use (premenopausal status, postmenopausal status, hormone [never use, past use, current use]), and BMI (<18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, ≥35 kg/m^2). Solid black line represents point estimate; dashed lines are 95% CIs.

Table 5. Multivariable RRs of Mortality According to Quintiles of Hip Circumference

	Hip Circumference, in					*P* for Linear Trend
	≤36	37–38	39	40–42	≥45	
Median, in	36	38	39	41	45	
Person-y	135 388	171 884	79 741	180 421	120 086	
All-cause mortality	744	795	326	903	739	
RR1 (age-adjusted)	1.0 (Ref)	0.80 (0.73–0.89)	0.68 (0.60–0.77)	0.79 (0.72–0.87)	0.97 (0.87–1.07)	0.987
RR2*	1.0 (Ref)	0.87 (0.79–0.96)	0.75 (0.66–0.86)	0.89 (0.80–0.98)	1.07 (0.96–1.19)	0.839
RR3 (model 2+BMI)	1.0 (Ref)	0.94 (0.84–1.04)	0.81 (0.71–0.93)	0.93 (0.83–1.04)	0.97 (0.83–1.12)	0.992
RR4 (model 2+WC)	1.0 (Ref)	0.81 (0.73–0.90)	0.66 (0.58–0.76)	0.70 (0.62–0.79)	0.70 (0.60–0.81)	0.002
RR5 (model 2+WC+BMI)	1.0 (Ref)	0.87 (0.78–0.97)	0.71 (0.62–0.82)	0.74 (0.67–0.87)	0.73 (0.62–0.86)	0.003
Smoking stratification†						
Never smokers	1.0 (Ref)	0.95 (0.77–1.17)	0.68 (0.52–0.89)	0.77 (0.61–0.97)	0.75 (0.57–0.99)	0.05
Ever smokers	1.0 (Ref)	0.73 (0.64–0.82)	0.62 (0.52–0.71)	0.61 (0.52–0.71)	0.61 (0.50–0.75)	<0.001
Age stratification, y†						
≤55	1.0 (Ref)	0.92 (0.77–1.10)	0.75 (0.59–0.96)	0.82 (0.65–1.02)	0.76 (0.57–1.01)	0.08
>55	1.0 (Ref)	0.86 (0.75–0.98)	0.71 (0.59–0.84)	0.77 (0.66–0.90)	0.75 (0.61–0.91)	0.04
Menopause stratification†						
Premenopausal	1.0 (Ref)	0.97 (0.75–1.25)	0.67 (0.47–0.96)	0.76 (0.55–1.04)	0.66 (0.44–1.01)	0.03
Postmenopausal	1.0 (Ref)	0.85 (0.75–0.96)	0.72 (0.61–0.84)	0.76 (0.67–0.88)	0.74 (0.62–0.89)	0.02
BMI stratification, kg/m^2†						
<25	1.0 (Ref)	0.92 (0.81–1.03)	0.79 (0.67–0.93)	0.91 (0.78–1.07)	0.86 (0.59–1.27)	0.271
≥25	1.0 (Ref)	1.30 (0.84–2.01)	1.00 (0.64–1.57)	0.99 (0.67–1.47)	0.91 (0.61–1.35)	0.373
CVD mortality	143	162	62	190	194	
RR1 (age-adjusted)	1.0 (Ref)	0.85 (0.68–1.06)	0.67 (0.50–0.90)	0.84 (0.68–1.05)	1.29 (1.04–1.59)	0.662
RR2*	1.0 (Ref)	0.92 (0.73–1.15)	0.75 (0.56–1.00)	0.95 (0.76–1.18)	1.40 (1.12–1.75)	0.471
RR3 (model 2+BMI)	1.0 (Ref)	1.00 (0.79–1.26)	0.79 (0.58–1.08)	0.90 (0.69–1.16)	0.90 (0.65–1.23)	0.336
RR4 (model 2+WC)	1.0 (Ref)	0.87 (0.69–1.10)	0.65 (0.47–0.89)	0.67 (0.51–0.87)	0.69 (0.51–0.94)	0.048
RR5 (model 2+WC+BMI)	1.0 (Ref)	0.94 (0.73–1.19)	0.70 (0.51–0.97)	0.72 (0.54–0.95)	0.62 (0.44–0.88)	0.005
Cancer mortality	323	407	178	471	369	
RR1 (age-adjusted)	1.0 (Ref)	0.96 (0.82–1.10)	0.86 (0.72–1.04)	0.97 (0.84–1.12)	1.13 (0.98–1.32)	0.211
RR2*	1.0 (Ref)	1.03 (0.89–1.19)	0.95 (0.79–1.14)	1.09 (0.94–1.26)	1.29 (1.11–1.51)	0.023
RR3 (model 2+BMI)	1.0 (Ref)	1.06 (0.91–1.23)	0.97 (0.81–1.18)	1.10 (0.93–1.29)	1.20 (0.98–1.49)	0.353
RR4 (model 2+WC)	1.0 (Ref)	0.97 (0.83–1.13)	0.85 (0.70–1.04)	0.91 (0.76–1.08)	0.95 (0.77–1.17)	0.430
RR5 (model 2+WC+BMI)	1.0 (Ref)	0.99 (0.85–1.16)	0.88 (0.72–1.07)	0.95 (0.79–1.13)	0.98 (0.78–1.24)	0.490
Mortality of obesity-related cancer‡	231	274	119	297	240	
RR1 (age-adjusted)	1.0 (Ref)	0.90 (0.75–1.07)	0.81 (0.65–1.01)	0.86 (0.72–1.02)	1.04 (0.86–1.24)	0.504
RR2*	1.0 (Ref)	0.98 (0.83–1.17)	0.91 (0.73–1.13)	0.99 (0.83–1.18)	1.23 (1.02–1.48)	0.018
RR3 (model 2+BMI)	1.0 (Ref)	1.02 (0.85–1.22)	0.94 (0.75–1.18)	1.02 (0.83–1.24)	1.19 (0.92–1.54)	0.241
RR4 (model 2+WC)	1.0 (Ref)	0.92 (0.77–1.11)	0.81 (0.64–1.03)	0.83 (0.67–1.02)	0.89 (0.69–1.14)	0.403
RR5 (model 2+WC+BMI)	1.0 (Ref)	0.96 (0.79–1.15)	0.84 (0.66–1.07)	0.88 (0.70–1.09)	0.95 (0.71–1.26)	0.671

Ref indicates reference. Values in parentheses are 95% CIs.

*Model 2 was adjusted for age (5-year interval), quintiles of physical activity, alcohol consumption (0, 0.1 to 4.9, 5.0 to 14.9, ≥15.0 g/d), family history of MI, smoking status (never, past, current [1 to 14, 15 to 24, 25+ cigarettes a day]), and menopausal status and hormone use (premenopausal status, postmenopausal status, and hormone never use, past use, and current use).

†RRs in stratified analyses were adjusted for factors in model 5 except the stratified factor.

‡Cancers thought to be linked with adiposity (colon cancer, breast cancer, pancreatic cancer, uterine, ovarian, and kidney cancer).

older women, abdominal adiposity was strongly and positively associated with all-cause mortality after adjustment for BMI. The follow-up time was short, and only findings related to WC were reported in the Danish cohort, whereas only findings for WHR were reported in the Swedish cohort. In a recent study of elderly women (75 years of age) in the United Kingdom,[8] WHR but not WC was positively related to mortality in nonsmoking women only, mainly because of cardiovascular mortality. By contrast, in a relatively small Dutch cohort of elderly women,[11] neither WHR nor WC was significantly associated with all-cause mortality. Data on the association of abdominal adiposity and fat distribution with

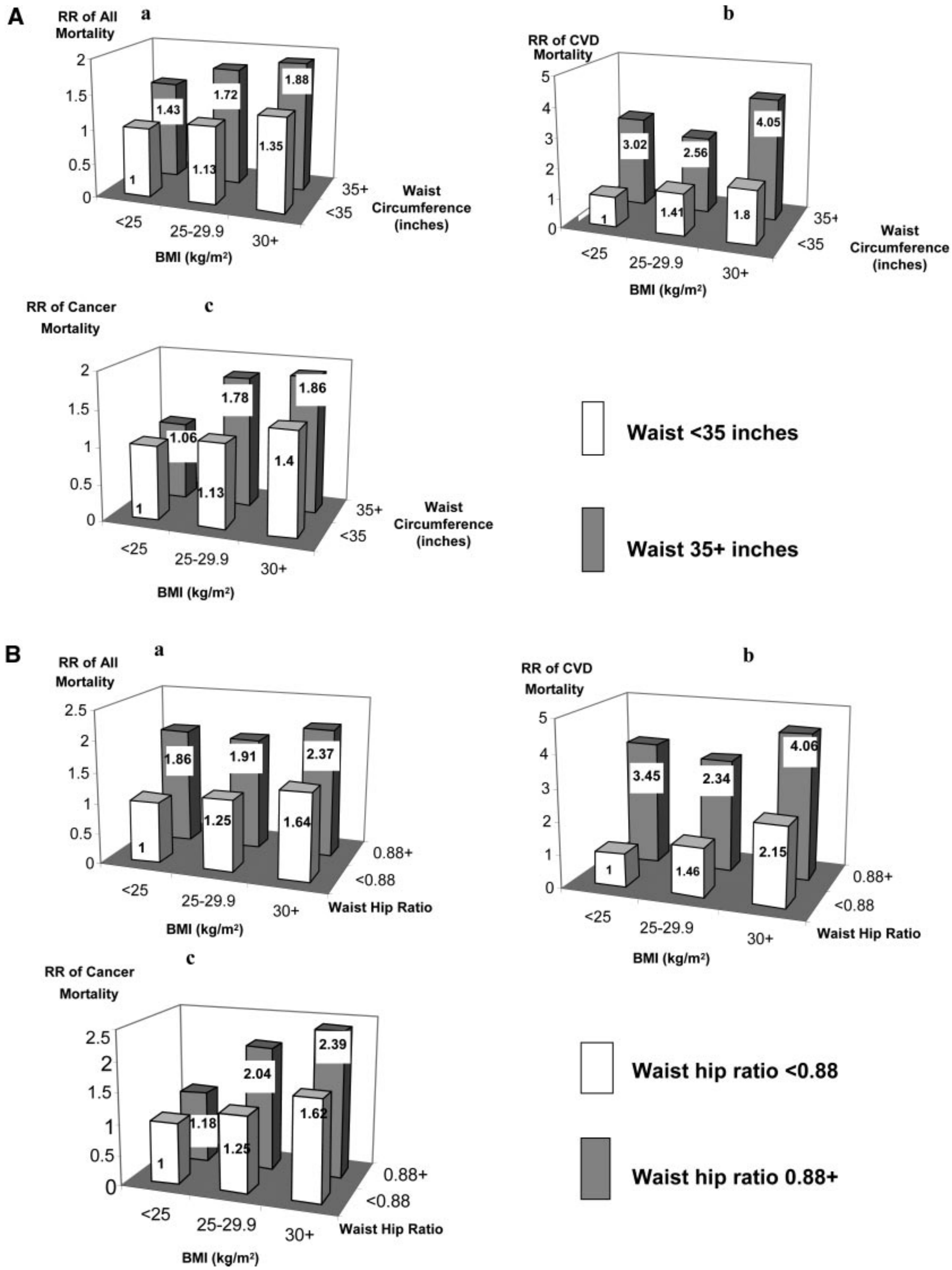


Figure 2. Multivariate RRs of all-cause, CVD, and cancer mortality according to joint classification of BMI and WC (A) or WHR (B) among never smokers. RRs are adjusted for age (5-year interval), quintiles of physical activity, alcohol consumption (0, 0.1 to 4.9, 5.0 to 14.9, ≥15.0 g/d), family history of MI, and menopausal status and hormone use (premenopausal status, postmenopausal status, hormone use [never use, past use, current use]).

overall cancer mortality are sparse. In the Iowa study,[9] neither WC nor WHR was significantly associated with cancer mortality after adjustment for multiple risk factors. Association of measures of abdominal adiposity with cancer mortality was not reported in most studies of abdominal adiposity and mortality.[8,10–12] With >600 000 person-years of follow-up and 3507 deaths, ours is one of the largest studies with the longest follow-up duration on abdominal adiposity and all-cause and cause-specific mortality.

The metabolic effects of abdominal adiposity are well established. Greater abdominal adiposity is closely associated with adverse metabolic profiles such as insulin resistance, dyslipidemia, and systematic inflammation, which play essential roles in the pathogenesis of CVD, diabetes mellitus, and certain cancers.[2,3] Of note, the association of abdominal obesity with these adverse metabolic profiles persisted among normal-weight women.[25] For instance, higher WC was significantly related to higher total cholesterol, low-density lipoprotein cholesterol and triglyceride levels, higher systolic and diastolic blood pressures, and higher fasting glucose levels among normal-weight women.

There have been continuous debates on whether WC or WHR is a better measure of abdominal adiposity in predicting health risks in epidemiological studies. WC as a measure of both subcutaneous and visceral fat can be measured easily. However, WC also is correlated with body frame size; thus, WHR often is used instead.[26] In the present study, both measures were significantly associated with all-cause, CVD, and cancer mortality. WHR did not seem to provide substantially better prediction than WC. Because WHR requires measures of both waist and hip circumference and is more difficult to interpret, WC is more applicable in clinical practice.

The inverse association of hip circumference with mortality (mainly CVD mortality) after adjustment for WC is of interest. It suggests that given a certain level of WC, a greater hip circumference, may be associated with lower CVD mortality. Such an association may be explained by larger peripheral fat mass associated with greater hip circumference.[7] Recent studies suggested that the femoral-gluteal fat depot, for a given amount of abdominal fat, plays a protective role by acting as a "sink" for circulating free fatty acids[27]; the femoral-gluteal region is more likely to effectively take up free fatty acids from the circulation and is less likely to release them readily.[7] Because of the increased free fatty acid uptake in the femoral-gluteal region resulting from a larger hip circumference, detrimental ectopic fat storage in tissues or organs (ie, the liver, skeletal muscle, and pancreas) and subsequent adverse metabolic effects may be prevented.[28] Indeed, studies using dual-energy x-ray absorptiometry or computed tomography to estimate fat and muscle content at the legs found that subcutaneous fat at the legs was associated with a more favorable cardiovascular risk profile (for a given amount of abdominal fat).[29–32]

Our study population consisted of registered nurses. The relative homogeneity in occupation and education can reduce confounding by socioeconomic factors. Because the study population was predominantly white, our findings require confirmation in other ethnic groups. In a recent study among Chinese women,[33] a significant positive association between WHR and mortality also was observed.

Conclusions

Our data indicate that abdominal adiposity is significantly and positively associated with all-cause and cause-specific mortality. Greater WC or WHR is associated with increased CVD mortality even in normal-weight women. Although maintaining a healthy weight should continue to be a cornerstone in the prevention of chronic diseases and premature death,[34] it is equally importanty to maintain a healthy waist size and prevent abdominal obesity.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In parallel with the increase in overall body adiposity in the US population, the prevalence of abdominal obesity increased substantially during the past decades. Evidence is growing that abdominal obesity is particularly detrimental to health. Greater abdominal adiposity is strongly related to an increased risk for cardiovascular disease and some other diseases independently of overall adiposity. In this study, we investigated several measures of abdominal adiposity, including waist circumference, waist-to-hip ratio, and waist-to-height ratio in relation to all-cause, cardiovascular disease, and cancer mortality during 16 years of follow-up in the Nurses' Health Study. With >600 000 person-years of follow-up and 3507 deaths, ours is one of the largest studies with the longest follow-up on abdominal adiposity and mortality. Our data indicate that anthropometric measures of abdominal adiposity were strongly and positively associated with all-cause, cardiovascular disease, and cancer mortality independently of body mass index. Elevated waist circumference and waist-to-hip ratio were associated with significantly increased cardiovascular disease mortality even among normal-weight women (body mass index, 18.5 to <25 kg/m^2). Although maintaining a healthy weight should continue to be a cornerstone in the prevention of chronic diseases and premature death, it is equally important to maintain a healthy waist size and to prevent abdominal obesity.

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