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A Pooled Analysis of Waist Circumference and Mortality in 650,000 Adults

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Abstract

Objective—To assess the independent impact of waist circumference on mortality across the entire range of body mass index (BMI), and to estimate the loss in life expectancy related to a higher waist circumference.

Methods—We pooled data from 11 prospective cohort studies with 650,386 white adults aged 20–83 years and enrolled from January 1, 1986 through December 31, 2000. We used proportional

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hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (95%CI) for the association of waist circumference with mortality.

Results—During a median follow-up of 9 years (maximum=21 years), 78,268 participants died. After accounting for age, study, BMI, smoking status, alcohol consumption, and physical activity, there was a strong positive linear association of waist circumference with all-cause mortality was observed for men (HR=1.52 for 110+ versus <90cm, 95%CI, 1.45–1.59; HR=1.07 per 5cm increment, 95%CI, 1.06–1.08) and women (HR=1.80 for 95+ versus <70cm, 95%CI, 1.70–1.89; HR=1.09 per 5cm increment, 95%CI, 1.08–1.09). The estimated decrease in life expectancy for highest versus lowest waist circumference was ~3 years for men and ~5 years for women. The HR per 5cm increment in waist circumference was similar for both sexes at all BMI levels from 20–50 kg/m^2, but it was higher at younger ages, higher for longer follow-up, and lower among male current smokers. The associations were stronger for heart and respiratory disease mortality than for cancer.

Conclusions—In white adults, higher waist circumference was positively associated with higher mortality at all levels of BMI from 20–50 kg/m^2. Waist circumference should be assessed in combination with BMI, even for those in the normal BMI range, as part of risk assessment for obesity-related premature mortality.

Increasing obesity, including central obesity, poses a major clinical and public health challenge due to elevated disease risks and premature mortality. Obesity is most commonly measured using body mass index (BMI), defined as weight in kilograms divided by the square of height in meters. Obese individuals (≥30.0 kg/m^2) have higher all-cause mortality than persons with normal BMI (18.5–24.9 kg/m^2).[1–6] However, in studies observing this association, lower BMI is also associated with higher mortality, resulting in a J or U-shaped risk curve. The shape of the BMI and mortality curve is explained in part by confounding due to tobacco use, pre-existing illness, recent weight loss or short duration of follow-up.[5] In addition, there are important limitations in using BMI as a measure of obesity because BMI does not discriminate fat from lean mass or abdominal from gluteofemoral fat, both of which have different health implications.[7] This partly explains the imperfect diagnostic accuracy of BMI in identifying individuals with excess body fat, particularly in the BMI range of 25–29.9 kg/m^2 and among men and the elderly.[8]

Waist circumference strongly correlates with abdominal obesity and is the most commonly used clinical measure of body fat distribution.[7,9] Waist circumference has been positively associated with all-cause mortality in most studies[3,10–17] with only a few exceptions.[18,19] Abdominal obesity appears to be more strongly associated with multiple chronic diseases than is gluteofemoral obesity, likely through adverse metabolic effects (e.g., decreased glucose tolerance, reduced insulin sensitivity, and adverse lipid profiles) of visceral relative to subcutaneous fat.[7,9,20]

The US Preventive Services Task Force[21] recommends screening for obesity based on a BMI of ≥30 kg/m^2, while the US National Institutes of Health[22] recommends only measuring waist circumference in people whose BMI is in the overweight (25.0–29.9 kg/m^2) or class I obesity range (30.0–34.9 kg/m^2), using clinically-defined cut-points of 102cm for men and 88cm for women to define elevated risk. However, measurement of waist circumference is not recommended for underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), or for grades II-III obesity (≥35.0 kg/m^2), although it has been noted that increased waist circumference may be a risk marker in persons of normal weight.[22] Because of the high correlation between BMI and waist circumference, it has been difficult for even the largest studies[3,16,17] to model the impact of waist circumference on mortality across all categories of BMI, and even those that have done this, the groupings of BMI were quite large. Given the established clinical utility of BMI, it is particularly important to fully understand the magnitude of risk of waist circumference within clinically meaningful categories of BMI.

To overcome these limitations, we examined the association of waist circumference with all-cause mortality in a pooled analysis of 650,000 participants from 11 prospective cohort studies. These pooled analyses included 78,000 deaths, which is five times larger than any individual study published to date.[3,16,17] This large sample size allowed us to (1) systematically model the association of waist circumference with mortality using clinically intuitive 5cm (~2 inch) increments for men and women, and (2) evaluate risk within relatively narrow bands of BMI to assess the validity of guidelines that use a single clinical cut-point for waist circumference and do not recommend monitoring waist circumference in underweight, normal, or extremely obese men and women.[22] We also estimated for the first time the potential years of life lost due to a large waist circumference.

METHODS

Study Cohorts

Prospective cohort studies from the BMI and mortality pooling project [5] were eligible for this analysis. All individual studies were approved by an institutional review board and participants provided informed consent. We excluded studies that did not collect waist circumference within 3 years of ascertaining baseline weight; all[10,11,14,17,23–26] but three[16,27,28] studies collected waist circumference at the same time as weight. Waist circumference was measured by a technician in one study,[14] while in the remaining studies it was reported by participants using measurement instructions and a paper tape provided by the study. The self-reported waist circumference data were found to be valid and reliable in several studies that formally assessed it.[28–30] All variables were harmonized across cohort studies as previously described.[5]

Participants were followed from study baseline (the year in which waist circumference was reported) to date of death, end of follow-up, or loss to follow-up. Cause of death was coded according to the *International Classification of Diseases* (9th or 10th revisions).

Statistical Analysis

We restricted the analysis to non-Hispanic white participants (based on self-report of race/ethnicity) and ages 20 to 84 years at baseline. We further excluded participants with a BMI of <15.0 kg/m^2 or ≥50.0 kg/m^2 and a waist circumference of ≤51cm or ≥190cm.

Waist circumference was categorized into six levels for men and seven levels for women, using sex-specific 5cm increments, with the lowest level of waist circumference as the reference group. Hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific mortality, stratified on study, were estimated by fitting Cox proportional hazards models with age as the underlying time metric. We adjusted for education, marital status, smoking status, alcohol consumption, physical activity and BMI (categories in eTable 1). We did not adjust for diabetes, prevalent heart disease, or hypertension to avoid bias introduced when adjusting for variables known to be on the causal pathway between abdominal obesity and mortality.[31] All analyses used sex-specific cutpoints and most results were presented separately for men and women, although we combined them for some analyses, with the highest two levels of waist circumference collapsed for women. We also modeled waist circumference as a continuous variable, reporting risk based on 5cm increments. We assessed heterogeneity between cohorts using the I^2 statistic.[32]

Years of life expectancy lost were derived using direct adjusted survival curves,[33] which is a simple extension of the proportional hazards framework (like that of a Kaplan-Meier curve) except that the survival curve uses age as the underlying time metric and adjusts for covariate differences. This method uses proportional hazards models to calculate survival curves for each individual and then averages them to obtain the survival curve for all men and for all women. Curves for each level of waist circumference were estimated by counterfactual; i.e., by applying the hazard coefficient for the waist circumference category to the sex-specific study population. This estimates survival as if assigning all participants within each sex alternately to one level of waist circumference or another. Life expectancy was estimated as the age at which 50% of the population would have been expected to have died according to the adjusted survival curve. The years of life gained/lost were calculated as the difference between the life expectancy for the group with a given waist circumference and that of the sex-specific reference group. Life expectancy analyses were restricted to participants whose ages were 40 or more years. All analyses were performed using SAS version 9.0 (SAS Institute).

RESULTS

Characteristics of Cohorts

We included 650,386 participants from 11 cohorts, with baseline years ranging from January 1, 1986 through December 31, 2000 (Table 1). The median age at baseline was 62 years; 58% of participants were female, and 52% were ever smokers. The mean BMI was 26.5±3.8 kg/m^2 for men and 25.3±4.7 kg/m^2 for women; the mean waist circumference was 97.4±10.5cm for men 81.5±13.1cm for women. For men, waist circumference was positively associated with BMI and former smoking status and negatively with physical activity, while it was only weakly associated with education and was not appreciably associated with prevalent disease, marital status or alcohol consumption (eTable 1). For women, waist circumference was associated with higher BMI and prevalent disease, while it was only weakly associated with smoking status, marital status, alcohol consumption and physical activity and was not appreciably associated with education. Waist circumference was correlated (Pearson r) with BMI for both men (r=0.77) and women (r=0.72).

Association with All-Cause Mortality

During 6.2 million person-years of follow-up (median=9, maximum=21 years), 78,268 deaths occurred (including 28,917 cancer, 24,411 CVD, and 6,202 respiratory disease deaths). Waist circumference was strongly and positively associated with all-cause mortality for both men and women in unadjusted models, and these associations were only slightly attenuated after adjustment for marital status, education, smoking status, alcohol consumption, and physical activity (Table 2). Further adjustment for height did not alter these associations (data not shown), while further adjustment for BMI led to a stronger and more linear association of the HR for waist circumference with mortality for both men and women (Table 2). Men with a waist circumference of 110+ cm had 52% greater mortality risk compared with those <90cm (HR=1.52; 95% CI, 1.45–1.59); women with a waist circumference ≥95cm had 80% greater mortality risk compared with those <70cm (HR, 1.80; 95% CI, 1.70–1.89). Each 5cm increment in waist circumference was associated with a 7% increased mortality risk for men (HR, 1.07; 95% CI, 1.06–1.08) and a 9% increased mortality risk for women (HR, 1.09; 95% CI, 1.08–1.09). The association of waist circumference with mortality was broadly similar with or without BMI adjustment for men at BMI <25 and 25–49.9 kg/m^2, while for women, BMI appeared to be a confounder for both BMI <25.0 kg/m^2 and 25–49.9 kg/m^2 (eFigure 1).

Our earlier pooled analysis of BMI and mortality[5] was restricted to never smokers and participants with no history of cancer or heart disease at each study's baseline to eliminate confounding by these factors. In this analysis, restriction on these factors had a relatively minor impact on the observed associations of waist circumference with mortality, particularly after adjustment for BMI (Figure 1). Based on these results, we elected to use all participants and to adjust for BMI in subsequent analyses.

Premature Mortality

eFigure 2 shows the expected loss in life expectancy, assuming a causal relation, for each level of waist circumference for men and women separately. For the highest level of waist circumference relative to the lowest level, the estimated decrease in life expectancy was ~3 years for men and ~5 years for women (Table 2).

Subgroup Analyses

To increase statistical power, we modeled waist circumference on a continuous scale using 5cm increments. While statistically significant heterogeneity in HRs was observed for individual studies, all estimates were qualitatively consistent in terms of effect size (eFigure 3). Statistically significant heterogeneity in several key subgroups defined on baseline age, smoking status, baseline CVD, and length of follow-up was also observed (Figure 2 and eTable 2), although overall estimates were qualitatively similar. While the association of waist circumference with all-cause mortality for both sexes was strongest for ages 20–49 and 50–59 years at baseline, even among men and women ages 70–84 years the HRs were elevated. HRs were similar by baseline CVD status for both sexes and by smoking status for women, but for men they were slightly weaker for current smokers. HRs were similar at <5, 5–9 and 10–14 years of follow-up, while the HRs were greater at 15+ years, particularly for men. For analyses stratified on baseline BMI, the HRs were of similar magnitude, with the

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exception of BMI <20 kg/m^2 for men, where the HR was below 1. The waist circumference association was strongest for deaths due to respiratory diseases in men and CVD for women, while deaths due to cancer showed the weakest (but still evident) associations for both sexes.

Joint Analysis

We next assessed the joint association of waist circumference and BMI with mortality for both sexes combined (Figure 3). Using the lowest category of waist circumference (<90cm for men and <70cm for women) and a BMI of 22.5–24.9 kg/m^2 as the reference group, we observed a strong, generally linear association of waist circumference with mortality within each category of BMI (note that Figure 3 excludes point estimates based on <100 deaths; complete data available in eTable 3). The highest HRs for waist circumference were observed at the extremes of BMI (<20 and 35.0+ kg/m^2), but clear increases in mortality risk were also observed for the normal BMI range (20.0–24.9 kg/m^2) and for overweight groups (25.0–27.4 and 27.5–29.9 kg/m^2). Results based on the NIH guideline cutpoints[22] (eTable 4) does not capture the graded risk that we identified in Figure 3.

Results were similar in sex-specific analyses (eFigure 4). With respect to cause of death, a similar pattern of increased risk of death with increasing waist circumference was observed within each category of BMI, with greater risks for CVD and respiratory disease mortality relative to cancer mortality (eFigure 5).

Discussion

In this pooled analysis of 11 cohort studies with over 650,000 participants we found a strong positive association of waist circumference in 5cm increments with total mortality after accounting for BMI, and this association was observed across a very wide range of BMI. This association remained after adjustment for a variety of demographic and lifestyle factors, physical activity and BMI, and held also for healthy never smokers. While broadly similar across almost all subgroups, the magnitude of risk was higher for younger ages and for longer lengths of follow-up, and was lower for current male smokers. Waist circumference was more strongly associated with CVD and respiratory disease mortality than cancer mortality.

Adjustment for BMI increased the linearity and strengthened the association of waist circumference with mortality, which has been reported previously.[3,12,13,15,17] Adjustment for BMI may decrease confounding by pre-existing diseases, pathologic conditions, or general frailty, all of which are associated with low lean body mass.[7] The analysis of the joint effect of waist circumference and BMI on mortality further supports the linear association for waist circumference after accounting for BMI. Indeed, the positive association of waist circumference with mortality was similar in magnitude across all categories of BMI from 20–50 kg/m^2 for men and 15–50 kg/m^2 for women. Finally, losses in life expectancy at age 40 were ~3 years for men and ~5 years for women when comparing those in the highest versus lowest waist circumference groups.

This study has several key strengths, including the largest sample size reported to date for assessing the association of waist circumference with mortality. This allowed us to estimate with high precision the association of waist circumference with mortality within narrow categories of BMI covering the entire range of BMI from 15–50 kg/m^2. We used standardized cutpoints and adjustment factors, and assessed the consistency across a wide range of study populations. We also assessed the impact of confounding by smoking and prevalent illness through stratification. Limitations include use of only a single measurement of waist circumference and BMI, and, except for one study,[14] waist circumference and BMI were self-reported. Self-reported waist circumference has been shown to be reasonably strongly correlated with measured waist circumference (r=0.80).[30,34] Typically it is under-reported by about 2–3cm but the degree of underreporting tends to increase with increasing circumference. These reporting errors likely resulted in under-estimation of the magnitude of the mortality risks in our study. While we were able to adjust for physical activity, we did not have an objective measure cardiorespiratory fitness, and therefore have incomplete adjustment for this potentially important confounder[35]; future studies should include such measures. Our results were restricted to white populations with a median age of 62 years at study baseline, and may not apply to the oldest old[36] or other racial/ethnic groups. While many studies have found superior survival for CVD patients with a higher BMI,[37] we observed similar associations for waist circumference and overall morality irrespective of baseline CVD, cautioning that our assessment was limited to self-report of any history of CVD.

Our pooled analysis of 11 studies had five times more deaths than any individual study published to date, which provided much greater precision and more importantly the ability to investigate the impact of waist circumference within narrow levels of BMI to assess independent effects. Our overall results are broadly consistent with those of other studies with more than 1000 deaths and not in this analysis.[3,12,13,15] The EPIC cohort[3] is the largest study not in this pooled analysis, with 359,387 participants and 14,723 deaths (versus 78,268 here); in EPIC, each 5cm increase in waist circumference was associated with a 17% increased risk of death for men (95% CI, 1.15–1.20) and a 13% increased risk of death for women (95% CI, 1.11–1.15). Our summary estimates were slightly lower, consistent with the older population of this study and the weaker association with increasing age.[38] Within EPIC the cross-classification of waist circumference by BMI was limited to 3 broad levels of BMI compared to 8 in our pooled analysis. This fine stratification enabled us to reduce the impact of residual variation in BMI on the waist circumference results and to examine the relationship of waist circumference in the severely obese (BMI >35 kg/m^2 (Figure 3)), for which EPIC had limited data. In a pooled analysis of 203,338 persons from 58 studies (1 from this analysis[11]), higher waist circumference was associated with higher coronary heart disease risk (7,750 cases) for each category of BMI divided into thirds.[39] In a meta-analysis of 58,609 people from 29 studies (3 from this analysis[14,24,25]), increased mortality risk (4,798 deaths) with higher waist circumference was observed in both healthy weight and overweight persons aged 65–74 years. These results are also broadly consistent with our findings. None of these previous studies estimated the reduction in life-expectancy associated with central adiposity.

Our results strongly suggest that BMI and waist circumference jointly serve as important predictors of mortality in the general population, so that clinically it may not be useful to try to select one measure over the other.[9,40] This also accords with recent work demonstrating that both measures have a complex association with metabolic syndrome risk factors.[41] There is also emerging evidence that modest exercise and a healthy diet are associated with reductions in metabolic risk profile, morbidity and mortality irrespective of weight status or weight change.[42] A majority of randomized trials have found that increased physical activity is associated with significant reductions in waist circumference or visceral fat despite either no change in weight or a change of $<3\%$.[42] Thus, management of excess waist circumference would be predicted to lower mortality across most BMI categories. Our results also suggest that current recommendations[22] regarding waist circumference, which are predicated on using a single sex-specific cutpoint and evaluation only in the BMI range of 25–34.9 kg/m^2, should be broadened as part of risk assessment for premature mortality. Our large sample size enabled us to detect a graded, linear increase in mortality risk across the full range of BMI including those within the normal and underweight category. The continuous association we observed makes it more difficult to define clinical cut-points for waist circumference, and suggests the importance of measuring waist circumference in more patients and implementing interventions to reduce larger circumferences (even among those with normal BMIs) and monitor trends to prevent increases over time.

Conclusion

In white adults, higher waist circumference was positively associated with higher mortality at all levels of BMI from 20–50 kg/m^2. Waist circumference should be assessed in combination with BMI, even for those in the normal BMI range, as part of risk assessment for obesity-related premature mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

BMI	body mass index

HR	hazard ratio
CI	confidence interval

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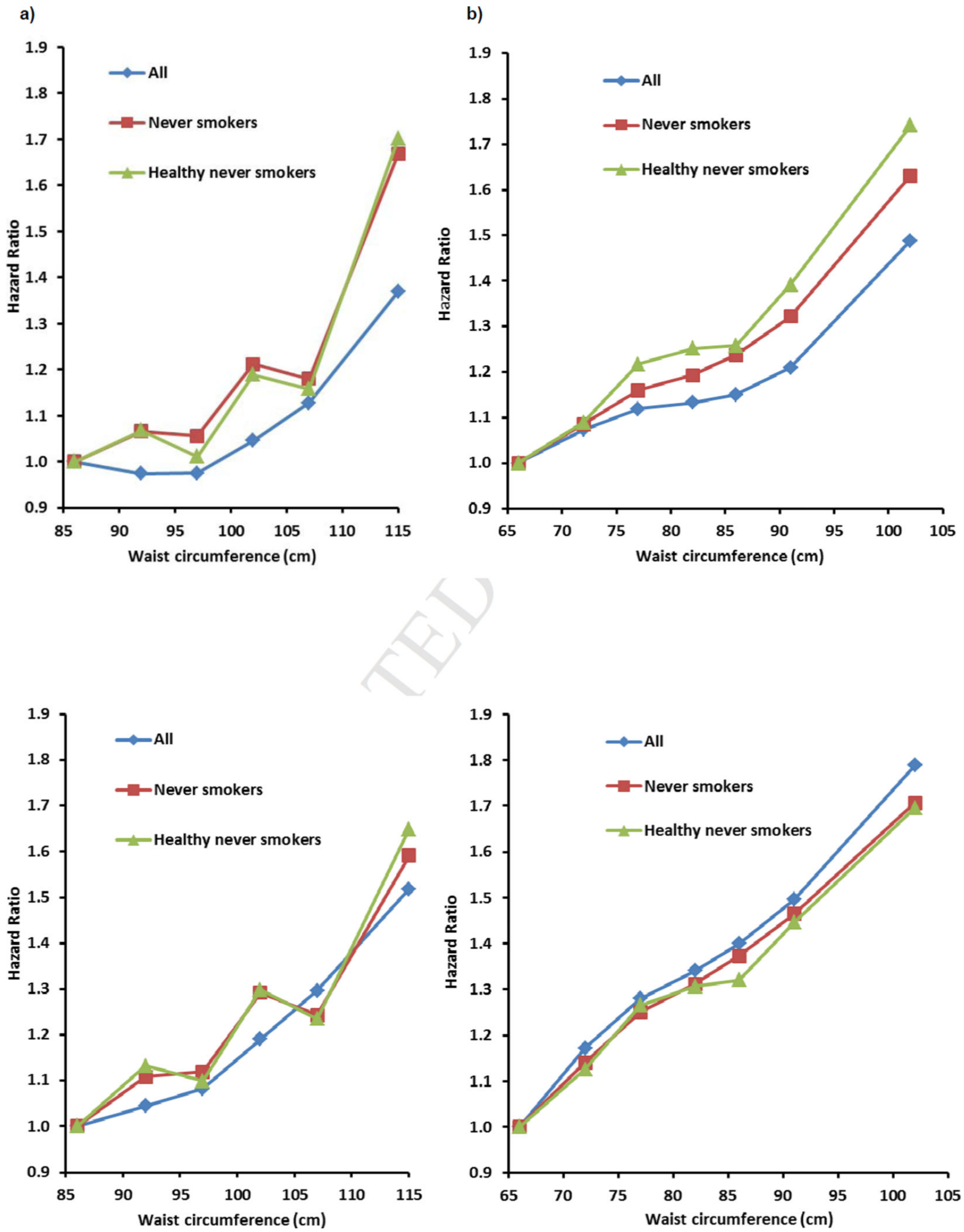

Figure 1.

Hazard Ratios for Waist Circumference and All-Cause Mortality: a) Men and b) Women, Adjusted for Education, Marital Status, Smoking Status, Alcohol Consumption and Physical Activity; c) Men and d) Women, Further Adjusted for BMI.

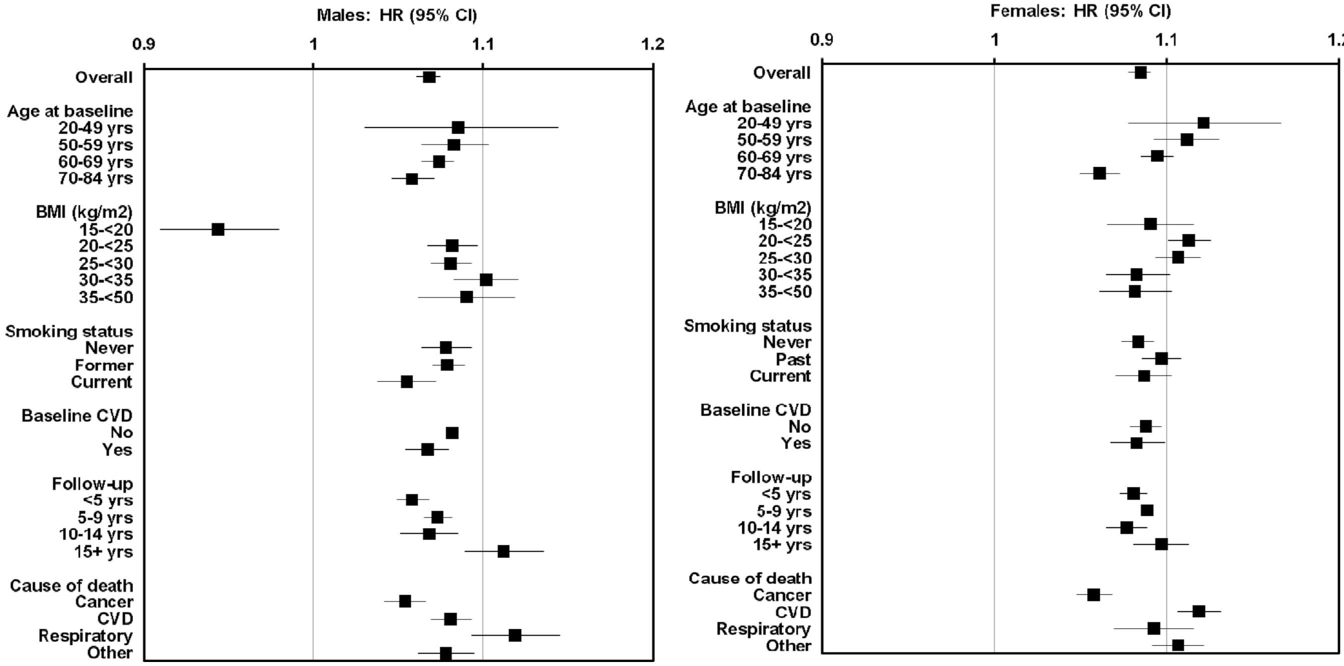

Figure 2.

Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Waist Circumference (per 5cm) and All-Cause Mortality, by Sex for Selected Subgroups.

Hazard ratios were calculated with age as the underlying time scale and stratified by study, and were adjusted for education, marital status, smoking, alcohol, physical activity and BMI

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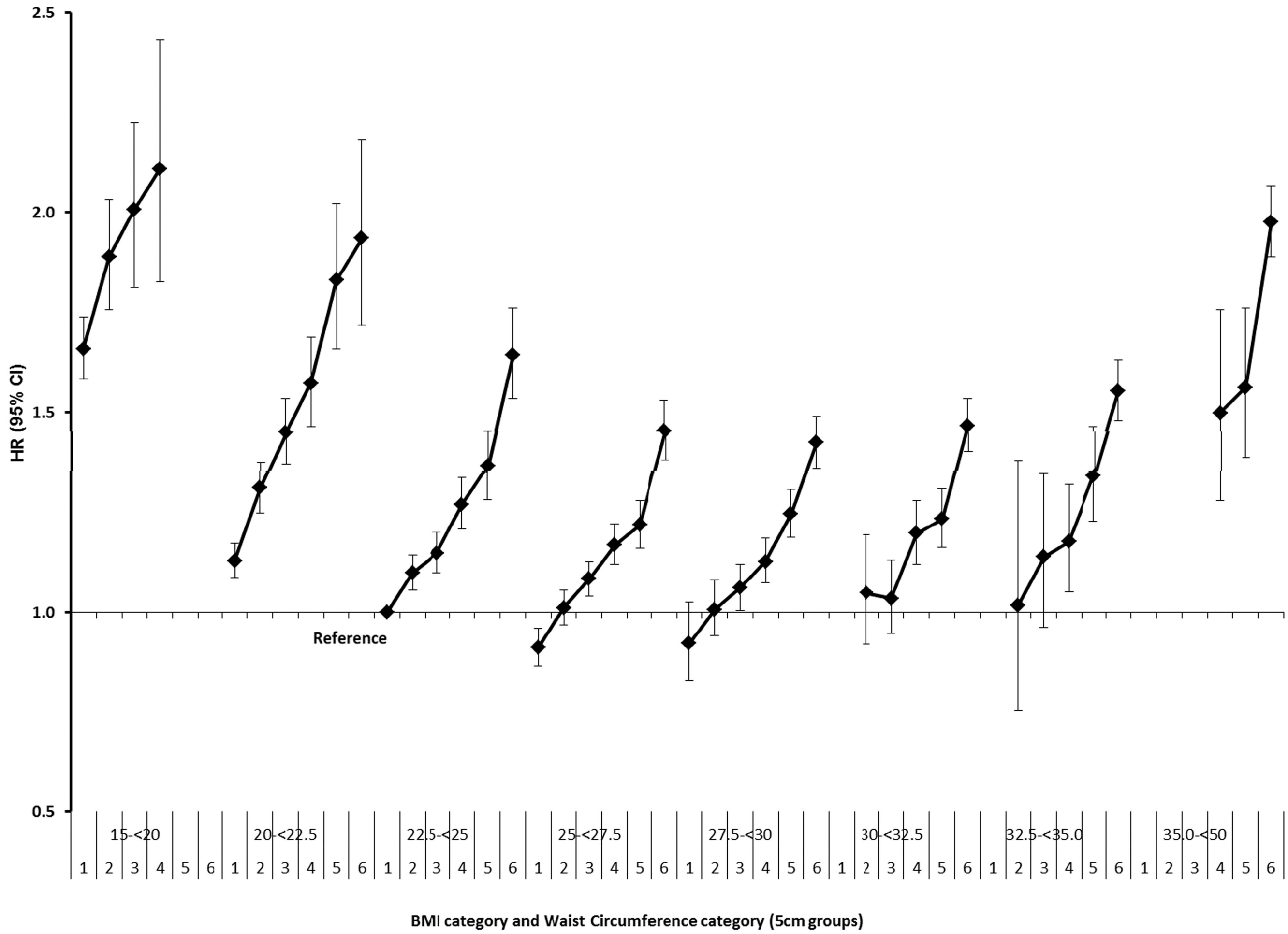

Figure 3.

Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Waist Circumference in 5cm Increments* and All-Cause Mortality by Body Mass Index (BMI) Category (Men and Women Combined), Adjusted for Education, Marital Status, Smoking Status, Alcohol Consumption, Physical Activity and BMI.

*Waist circumference cutpoints (cm) for men <90.0, 90.0–94.9, 95.0–99.9, 100.0–104.9, 105.0–109.9, 110.0+ and women <70.0, 70.0–74.9, 75.0–79.9, 80.0–84.9, 85.0–89.9, 90.0+.

TABLE 1

Cohort Characteristics for the Pooled Analysis of Waist Circumference and Mortality

Study	Sex	N	Year study entry	Follow-up (years) Median (max)	Age at entry (yrs) Median (range)	BMI, kg/m^2 Mean (SD)	Waist, cm Mean (SD)	Ever Smoker	Baseline CA or CVD[a]	Deaths
NIH-AARP Diet and Health Study (AARP) [16]	Combined	217428	1996–1997	9 (10)	63 (51–72)					21413
	Women	83066				25.8 (5.0)	85 (13)	53%	13%	6085
	Men	134362				26.9 (3.9)	98 (11)	66%	21%	15328
BCDDP[b] Follow-up Study (BCDDP) [23]	Women	25950	1993–1995	3 (5)	66 (46–83)	25.4 (4.6)	82 (12)	45%	26%	3849
California Teachers Study (CTS) [28]	Women	71374	1997–2000	7 (8)	55 (25–83)	24.4 (4.6)	82 (13)	34%	26%	2524
Cohort of Swedish Men (COSM) [25]	Men	34098	1998	9 (9)	60 (46–80)	25.7 (3.3)	96 (10)	62%	38%	4298
Cancer Prevention Study-II (CPS-II) [17]	Combined	120407	1997–1999	10 (11)	68 (45–83)					20561
	Women	64941				25.7 (4.8)	86 (13)	44%	23%	8125
	Men	55466				26.5 (3.7)	99 (10)	66%	36%	12436
Health Professionals Follow-up Study (HPFS) [11]	Men	29688	1987	16 (21)	56 (40–78)	25.3 (3.0)	95 (9)	53%	34%	6460
Iowa Women's Health Study (IWHS) [10]	Women	37937	1986	18 (19)	62 (53–71)	26.1 (4.8)	69 (11)	34%	17%	10545
Melbourne Collaborative Cohort Study (MCCS) [14]	Combined	41323	1990–1994	15 (19)	56 (28–81)					4763
	Women	24374				26.7 (4.9)	80 (12)	31%	8%	2087
	Men	16949				27.2 (3.6)	94 (10)	59%	8%	2676
NYU Women's Health Study (NYUWHS) [27]	Women	7279	1986–1991	17 (19)	54 (34–73)	24.5 (4.3)	74 (12)	55%	8%	715
Swedish Mammography Cohort (SMC) [24]	Women	29955	1998	9 (9)	61 (49–83)	25.0 (3.9)	84 (11)	45%	34%	2342
Women's Lifestyle and Health Study (WLHS) [26]	Women	34947	1991–1992	16 (16)	40 (30–50)	23.4 (3.5)	77 (9)	57%	10%	798
Summary	Combined	650386	1986–2000	9 (21)	62 (25–83)					78268
	Women	379823	1986–2000	9 (19)	61 (25–83)	25.3 (4.7)	81.5 (13.1)	44%	19%	37070
	Men	270563	1987–1999	9 (21)	64 (28–83)	26.5 (3.8)	97.4 (10.5)	64%	27%	41198

[a] Prevalent cancer (CA) or cardiovascular disease (CVD) at study baseline.

[b] Breast Cancer Detection Demonstration Project.

TABLE 2

Association of Waist Circumference with All-Cause Mortality, Pooled Analysis of 11 Cohort Studies

	Category of Waist Circumference							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**P-trend**
Men								
Cutpoint (cm)	<90.0	90.0–94.9	95.0–99.9	100.0–104.9	105.0–109.9	110.0+		
Median of group (cm)	86.4	92.0	96.5	101.6	106.7	115.0		
N	61,442	57,867	53,780	39,134	27,308	31,032		
Deaths	7939	7977	7806	6291	4834	6351		
Person-years	618,574	567,777	519,551	369,595	252,139	279,799		
Rate[a]	474	450	468	543	615	767		
Hazard Ratio (95% CI)								
Basic model[b]	1 (reference)	0.98 (0.95, 1.01)	0.99 (0.96, 1.02)	1.10 (1.06, 1.13)	1.22 (1.18, 1.27)	1.56 (1.51, 1.61)		<0.0001
Multivariate-adjusted[c]	1 (reference)	0.97 (0.94, 1.01)	0.98 (0.95, 1.01)	1.05 (1.01, 1.08)	1.13 (1.09, 1.17)	1.37 (1.32, 1.42)		<0.0001
Further adjusted for BMI[d]	1 (reference)	1.04 (1.01, 1.08)	1.08 (1.05, 1.12)	1.19 (1.15, 1.24)	1.30 (1.24, 1.35)	1.52 (1.45, 1.59)		<0.0001
Life expectancy	85.5	85.2	85.0	84.0	83.5	82.4		
Years of life lost	0	0.3	0.5	1.5	2.0	3.1		
Women								
Cutpoint (cm)	<70.0	70.0–74.9	75.0–79.9	80.0–84.9	85.0–89.9	90.0–94.9	95.0+	
Median of group (cm)	66.0	72.4	77.0	81.9	86.4	91.4	101.6	
N	67,862	62,287	57,755	56,353	44,452	32,878	58,236	
Deaths	7918	4940	4821	4984	4140	3322	6945	
Person-years	795,238	637,511	573,935	530,947	403,653	291,844	502,015	
Rate[a]	362	345	348	345	348	388	455	
Hazard Ratio (95% CI)								
Basic model[b]	1 (reference)	1.07 (1.03, 1.11)	1.12 (1.08, 1.17)	1.15 (1.11, 1.20)	1.19 (1.14, 1.24)	1.27 (1.21, 1.33)	1.62 (1.56, 1.69)	<0.0001
Multivariate-adjusted[c]	1 (reference)	1.07 (1.03, 1.11)	1.12 (1.08, 1.16)	1.13 (1.09, 1.18)	1.15 (1.10, 1.20)	1.21 (1.16, 1.27)	1.49 (1.43, 1.55)	<0.0001
Further adjusted for BMI[d]	1 (reference)	1.17 (1.13, 1.22)	1.28 (1.23, 1.33)	1.34 (1.29, 1.40)	1.40 (1.34, 1.47)	1.50 (1.42, 1.58)	1.79 (1.70, 1.89)	<0.0001
Life expectancy	90.5	89.5	88.5	88.2	87.8	87.5	85.5	
Years of life lost	0	1.0	2.0	2.3	2.7	3.0	5.0	

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

[b] Hazard ratios were calculated with age as the underlying time scale and stratified by study.

[c] Further adjusted for education, marital status, smoking status, alcohol consumption, and physical activity

[d] Further adjusted for BMI (categorical)

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