ORIGINAL ARTICLE

General and Abdominal Adiposity and Risk of Death in Europe

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ABSTRACT

BACKGROUND

Previous studies have relied predominantly on the body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) to assess the association of adiposity with the risk of death, but few have examined whether the distribution of body fat contributes to the prediction of death.

METHODS

We examined the association of BMI, waist circumference, and waist-to-hip ratio with the risk of death among 359,387 participants from nine countries in the European Prospective Investigation into Cancer and Nutrition (EPIC). We used a Cox regression analysis, with age as the time variable, and stratified the models according to study center and age at recruitment, with further adjustment for educational level, smoking status, alcohol consumption, physical activity, and height.

RESULTS

During a mean follow-up of 9.7 years, 14,723 participants died. The lowest risks of death related to BMI were observed at a BMI of 25.3 for men and 24.3 for women. After adjustment for BMI, waist circumference and waist-to-hip ratio were strongly associated with the risk of death. Relative risks among men and women in the highest quintile of waist circumference were 2.05 (95% confidence interval [CI], 1.80 to 2.33) and 1.78 (95% CI, 1.56 to 2.04), respectively, and in the highest quintile of waist-to-hip ratio, the relative risks were 1.68 (95% CI, 1.53 to 1.84) and 1.51 (95% CI, 1.37 to 1.66), respectively. BMI remained significantly associated with the risk of death in models that included waist circumference or waist-to-hip ratio ($P<0.001$).

CONCLUSIONS

These data suggest that both general adiposity and abdominal adiposity are associated with the risk of death and support the use of waist circumference or waist-to-hip ratio in addition to BMI in assessing the risk of death.

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Abdominal obesity is more closely associated with the risk of several chronic diseases than is gluteofemoral obesity, and large studies have suggested that waist circumference or the waist-to-hip ratio, as indicators of abdominal obesity, may be better predictors of the risk of disease than the body-mass index (BMI, the weight in kilograms divided by the square of the height in meters), an indicator of general adiposity.[1-4] Current guidelines with respect to obesity recommend the measurement of waist circumference in persons with a BMI between 25.0 and 34.9 and propose cutoff points for waist circumference of 102 cm in men and 88 cm in women (and cutoff points for waist-to-hip ratio of 1.0 in men and 0.85 in women) to define abdominal obesity and to identify persons at risk for disease.[2] However, less is known about the association of waist circumference or waist-to-hip ratio with the risk of death.

Most studies that have examined the association of both general and abdominal obesity with the risk of death[5-16] have shown that abdominal adiposity is an important predictor of the risk of death, but few such studies were conducted in Europe.[14-16] Large studies in the United States and Korea either did not assess waist circumference or waist-to-hip ratio[17,18] or relied on self-reports of anthropometric measurements.[12,19] We therefore evaluated the association of general and abdominal adiposity with the risk of death in the European Prospective Investigation into Cancer and Nutrition (EPIC), a large cohort study in Europe.

METHODS

STUDY POPULATION

EPIC includes 519,978 men and women who were 25 to 70 years of age at enrollment (during the period from 1992 through 2000) and who were recruited predominantly from the general population residing in a given geographic area (town or province) in 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) (see Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org).[20] Participants gave written informed consent, underwent anthropometric measurements, and completed a questionnaire that asked for information regarding sociodemographic and lifestyle characteristics, medical history, alcohol consumption, and physical activity.[20-22] Approval was obtained from the ethics review board of the International Agency for Research on Cancer and the local review boards of the participating institutions. The association of anthropometric measures with the risk of death has previously been reported in two cohorts that are part of EPIC — those in Denmark and Malmö, Sweden.[15,16] These participants are included in the present analysis with longer follow-up periods.

We excluded 2088 participants who withdrew from the study and for whom there was no follow-up information on vital status. Furthermore, the cohort in Umeå, Sweden (25,720 persons), was excluded because the information on leisure-time physical activity provided on the questionnaire completed by this cohort was not compatible with that provided on the other EPIC questionnaires. We also excluded subjects for whom data on measured height or weight were missing — all the participants from the Norwegian cohorts (37,205 persons), 52,872 participants from the French cohorts, and 8451 from other cohorts. In addition, we excluded 1441 participants with missing questionnaire data and, to reduce the effect of implausible extreme values, 7659 participants who were in the top or bottom 1% of the total cohort with respect to the ratio of energy intake to estimated energy requirement.[23] Finally, to avoid confounding by preexisting chronic diseases, we excluded 25,155 participants who reported a history of cancer, heart disease, or stroke at baseline. Thus, the final study included 359,387 participants.

ASSESSMENT OF END POINTS

Vital status and the cause and date of death were ascertained by means of record linkages with cancer registries, boards of health, and death indexes (in the case of Denmark, Italy, the Netherlands, Spain, Sweden, and the United Kingdom) or by active follow-up (in the case of Germany, Greece, and France). Active follow-up included inquiries by mail or telephone to participants, municipal registries, regional health departments, physicians, and hospitals. Data on death were coded according to the rules of the *International Classification of Diseases, 10th Revision* (ICD-10). The code for the underlying cause of death was used, classified as circulatory (ICD-10 codes I00 through I99), neoplasms (C00 through D48), respiratory (J00 through J99 [i.e., not including neoplasms of the respiratory organs]), other, or not reported.

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ASSESSMENT OF ANTHROPOMETRIC DATA

Weight and height were measured with subjects not wearing shoes.[24] Waist circumference was measured either at the narrowest circumference of the torso or at the midpoint between the lower ribs and the iliac crest. Hip circumference was measured horizontally at the level of the largest lateral extension of the hips or over the buttocks. Each participant's body weight and waist and hip circumferences were corrected for the clothing worn during measurement in order to reduce heterogeneity due to protocol differences among centers (see Appendix 1 in the Supplementary Appendix for a detailed description). Measurements of waist circumference and waist-to-hip ratio were missing for 3833 participants (1.07%) and 6466 participants (1.80%), respectively. These participants were excluded from analyses of these variables.

STATISTICAL ANALYSIS

Associations between anthropometric variables and the risk of death were analyzed with the use of a Cox regression model, with age as the underlying time variable. We divided the cohort into categories of BMI that were similar to those used for the National Institutes of Health–AARP cohort (<18.5, 18.5 to <21.0, 21.0 to <23.5, 23.5 to <25.0, 25.0 to <26.5, 26.5 to <28.0, 28.0 to <30.0, 30.0 to <35.0, and ≥35.0).[17] These categories incorporate current definitions of underweight (BMI, <18.5), normal weight (18.5 to <25.0), overweight (25.0 to <30.0), and obesity (≥30.0).[2] The likelihood-ratio test was used to assess the statistical significance of an asssociation between BMI and the risk of death. In addition, subjects were grouped into sex-specific quintiles according to waist circumference and waist-to-hip ratio. Tests for trend in relative risks were based on medians across quintiles. The relationships were also evaluated with the use of nonparametric restricted cubic splines,[25] with 4 knots defined at the 5th, 25th, 75th, and 95th percentiles of the anthropometric measurements. All models were stratified according to age at recruitment and according to study center to reduce violations of the proportional-hazards assumption. The analysis was further adjusted for smoking status, educational level, alcohol consumption, physical activity, and height. Models for waist circumference and waist-to-hip ratio were also adjusted for BMI.

Subgroup analyses were conducted according to strata of smoking status and age at recruitment. Waist circumference and waist-to-hip ratio were also examined across sex-specific BMI thirds. Tests for interaction were performed with the likelihood-ratio test of models with and without interaction terms. Differences according to the cause of death were examined in competing risk models.[26] Similar analyses examined differences between models that censored follow-up time after 5 years and models that excluded person-time and events from the first 5 years.

To assess performance in the prediction of death, we calculated the C statistic, the Hosmer–Lemeshow statistic, Nagelkerke's generalized-model R^2 statistic, and net reclassification indexes for a follow-up time of 5 years (available for 98.2% of the cohort), using logistic-regression models, adjusted for the covariates described above.[27-31]

All P values presented are two-tailed, and P values of less than 0.05 were considered to indicate statistical significance. Analyses were performed with the use of SAS software, version 9.1 (SAS Institute).

RESULTS

CHARACTERISTICS OF STUDY PARTICIPANTS

During a mean (±SD) follow-up of 9.7±2.0 years, 14,723 of the initial 359,387 participants died (5429 from neoplasms, 3443 from circulatory causes, 637 from respiratory causes, 2209 from other causes, and 3005 from unspecified causes; see Table 1 in the Supplementary Appendix). The mean age at baseline was 51.5±10.4 years; 65.4% of the participants were women. Participants with a higher BMI, as compared with those who had a lower BMI, were older, were less likely to be current smokers, and had a lower educational level (see Table 2 in the Supplementary Appendix). Alcohol consumption was positively related to BMI among men but inversely related to BMI among women. Pearson partial-correlation coefficients, adjusted for age and study center, for the correlation of BMI with waist circumference and with waist-to-hip ratio were 0.85 and 0.55, respectively, among men and 0.84 and 0.38, respectively, among women (P<0.001 for all correlations).

ASSOCIATIONS WITH THE RISK OF DEATH

There was a significant nonlinear association of BMI with the risk of death, with the lowest risks at a BMI of 25.3 among men and 24.3 among women, and increased risks in the lower and upper BMI categories (Table 1 and Fig. 1). These

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Table 1. Relative Risk of Death According to BMI among Men and Women in the European Prospective Investigation into Cancer and Nutrition.*

Relative Risk	BMI				
Men	<18.5	18.5 to <21.0	21.0 to <23.5	23.5 to <25.0	25.0 to <26.5
Person-years	4504	45,494	176,701	188,823	215,370
Deaths (no.)	92	390	1071	1144	1209
Overall relative risk (95% CI)					
Crude§	2.86 (2.30–3.57)	1.64 (1.46–1.84)	1.08 (0.99–1.17)	1.00	0.90 (0.83–0.98)
Adjusted¶	2.30 (1.84–2.86)	1.39 (1.24–1.57)	1.03 (0.94–1.12)	1.00	0.91 (0.84–0.99)
Relative risk by subgroup (95% CI)¶					
Smoking status‖					
Never smoked	1.19 (0.54–2.62)	1.25 (0.93–1.67)	0.97 (0.80–1.07)	1.00	0.89 (0.73–1.07)
Former smoker	2.18 (1.39–3.41)	1.69 (1.34–2.13)	1.05 (0.90–1.22)	1.00	0.95 (0.83–1.09)
Current smoker	2.75 (2.09–3.63)	1.39 (1.19–1.63)	1.03 (0.91–1.17)	1.00	0.86 (0.76–0.98)
Age					
<55 yr	4.43 (3.01–6.54)	1.66 (1.33–2.07)	1.07 (0.90–1.26)	1.00	1.09 (0.93–1.28)
55 to <65 yr	2.27 (1.55–3.33)	1.30 (1.09–1.55)	1.03 (0.91–1.17)	1.00	0.83 (0.73–0.93)
≥65 yr	1.56 (1.07–2.27)	1.32 (1.06–1.65)	1.00 (0.85–1.17)	1.00	0.91 (0.77–1.06)
Follow-up**					
≤5 yr	3.08 (2.26–4.20)	1.29 (1.06–1.57)	1.02 (0.89–1.17)	1.00	0.84 (0.73–0.96)
>5 yr	1.78 (1.30–2.45)	1.45 (1.25–1.68)	1.03 (0.93–1.15)	1.00	0.95 (0.86–1.05)
Cause of death					
Neoplasms	1.20 (0.73–1.97)	1.27 (1.03–1.55)	0.92 (0.80–1.07)	1.00	0.82 (0.72–0.95)
Circulatory	1.84 (1.19–2.87)	1.05 (0.81–1.36)	0.97 (0.81–1.15)	1.00	0.95 (0.80–1.12)
Respiratory	6.53 (3.56–11.97)	2.29 (1.46–3.59)	1.21 (0.84–1.76)	1.00	0.66 (0.44–0.99)
Other	4.67 (2.98–7.31)	2.02 (1.54–2.66)	1.30 (1.05–1.60)	1.00	0.99 (0.80–1.22)
Women					
Person-years	41,623	286,794	574,777	344,116	287,155
Deaths (no.)	167	714	1397	953	865
Overall relative risk (95% CI)					
Crude§	1.96 (1.66–2.32)	1.27 (1.15–1.40)	1.01 (0.93–1.10)	1.00	1.01 (0.92–1.11)
Adjusted¶	1.71 (1.44–2.01)	1.22 (1.10–1.34)	1.00 (0.92–1.09)	1.00	1.01 (0.92–1.11)
Relative risk by subgroup (95% CI)¶					
Smoking status‖					
Never smoked	1.44 (1.08–1.92)	1.09 (0.93–1.27)	1.00 (0.88–1.13)	1.00	1.00 (0.87–1.15)
Former smoker	1.47 (0.98–2.20)	1.01 (0.82–1.25)	0.85 (0.72–1.00)	1.00	0.94 (0.79–1.12)
Current smoker	2.29 (1.79–2.95)	1.53 (1.29–1.81)	1.14 (0.98–1.33)	1.00	1.07 (0.90–1.28)
Age					
<55 yr	1.69 (1.26–2.27)	1.15 (0.97–1.37)	0.96 (0.82–1.11)	1.00	1.04 (0.87–1.25)
55 to <65 yr	1.92 (1.49–2.48)	1.26 (1.08–1.47)	1.01 (0.89–1.15)	1.00	0.97 (0.84–1.12)
≥65 yr	1.40 (1.01–1.96)	1.28 (1.05–1.56)	1.04 (0.89–1.23)	1.00	1.04 (0.87–1.24)
Follow-up **					
≤5 yr	2.01 (1.51–2.68)	1.17 (0.97–1.40)	1.07 (0.92–1.24)	1.00	0.99 (0.84–1.16)
>5 yr	1.56 (1.27–1.92)	1.24 (1.10–1.40)	0.97 (0.88–1.08)	1.00	1.02 (0.91–1.14)
Cause of death					
Neoplasms	1.16 (0.85–1.58)	1.17 (1.00–1.36)	0.98 (0.86–1.11)	1.00	1.00 (0.87–1.15)
Circulatory	1.09 (0.69–1.75)	1.10 (0.87–1.41)	1.01 (0.83–1.22)	1.00	1.13 (0.92–1.39)
Respiratory	4.74 (2.60–8.64)	1.70 (1.05–2.76)	1.29 (0.85–1.97)	1.00	0.64 (0.37–1.11)
Other	2.97 (2.07–4.27)	1.43 (1.10–1.84)	1.11 (0.89–1.39)	1.00	1.02 (0.79–1.31)

* BMI denotes body-mass index, which is the weight in kilograms divided by the square of the height in meters. CI denotes confidence interval.

† P values, based on the likelihood-ratio test, are for comparisons of the model that included BMI categories with the model that did not include BMI categories, with 8 degrees of freedom.

‡ P values, based on the likelihood-ratio test, are for comparisons of the model that included interaction terms between BMI and the stratification variable with the model that did not include these interaction terms (with 16 degrees of freedom each for smoking status and age, 24 degrees of freedom for cause of death, and 8 degrees of freedom each for preexisting disease and length of follow-up); for cause of death and length of follow-up, the data-augmentation method described by Lunn and McNeil was used.[26]

§ The crude relative risk was calculated with the use of Cox proportional-hazards regression, with age as the underlying time variable and stratification according to center and age at recruitment.

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BMI				P Value†	P Value for Interaction‡
26.5 to <28.0	28.0 to <30.0	30.0 to <35.0	≥35.0		
186,758	177,458	157,899	24,794		
1118	1212	1256	313		
0.95 (0.88–1.03)	1.09 (1.01–1.18)	1.28 (1.18–1.39)	2.06 (1.81–2.34)	<0.001	
0.96 (0.88–1.04)	1.08 (1.00–1.17)	1.24 (1.14–1.35)	1.94 (1.71–2.20)	<0.001	
					0.09
1.05 (0.86–1.27)	1.21 (1.01–1.47)	1.48 (1.22–1.79)	2.78 (2.09–3.71)	<0.001	
1.01 (0.88–1.15)	1.16 (1.01–1.32)	1.39 (1.21–1.59)	2.10 (1.71–2.58)	<0.001	
0.91 (0.80–1.03)	0.99 (0.87–1.13)	1.11 (0.98–1.26)	1.66 (1.34–2.05)	<0.001	
					0.004
0.91 (0.77–1.08)	1.16 (0.98–1.37)	1.41 (1.20–1.66)	1.98 (1.55–2.53)	<0.001	
0.97 (0.86–1.09)	1.06 (0.94–1.19)	1.22 (1.08–1.37)	2.02 (1.69–2.41)	<0.001	
0.99 (0.84–1.16)	1.06 (0.90–1.24)	1.10 (0.93–1.30)	1.63 (1.21–2.19)	<0.001	
					0.13
0.93 (0.81–1.07)	1.06 (0.93–1.21)	1.16 (1.02–1.33)	1.71 (1.38–2.11)	<0.001	
0.98 (0.88–1.09)	1.09 (0.99–1.21)	1.29 (1.16–1.43)	2.09 (1.78–2.46)	<0.001	
					<0.001
0.91 (0.79–1.04)	0.93 (0.81–1.07)	0.94 (0.82–1.09)	1.24 (0.97–1.60)	0.002	
1.01 (0.85–1.20)	1.28 (1.09–1.51)	1.62 (1.38–1.90)	2.70 (2.13–3.42)	<0.001	
0.74 (0.49–1.10)	0.74 (0.50–1.11)	0.90 (0.60–1.34)	1.65 (0.90–3.03)	<0.001	
0.94 (0.75–1.17)	1.12 (0.90–1.40)	1.26 (1.01–1.57)	2.15 (1.57–2.96)	<0.001	
221,840	209,676	250,494	85,953		
745	734	926	417		
1.08 (0.98–1.19)	1.10 (1.00–1.21)	1.18 (1.08–1.29)	1.68 (1.49–1.89)	<0.001	
1.07 (0.97–1.18)	1.11 (1.00–1.22)	1.17 (1.07–1.29)	1.65 (1.46–1.85)	<0.001	
					0.04
1.12 (0.98–1.30)	1.12 (0.97–1.29)	1.25 (1.09–1.43)	1.80 (1.53–2.12)	<0.001	
0.91 (0.75–1.11)	0.94 (0.77–1.14)	0.95 (0.79–1.16)	1.49 (1.16–1.91)	0.002	
1.21 (1.00–1.46)	1.30 (1.07–1.58)	1.38 (1.14–1.67)	1.60 (1.20–2.13)	<0.001	
					0.79
1.06 (0.87–1.28)	1.16 (0.96–1.41)	1.24 (1.03–1.50)	1.66 (1.31–2.11)	<0.001	
1.03 (0.89–1.19)	1.16 (1.01–1.33)	1.19 (1.03–1.36)	1.68 (1.42–2.00)	<0.001	
1.15 (0.96–1.37)	1.00 (0.83–1.21)	1.10 (0.93–1.31)	1.56 (1.24–1.97)	0.002	
					0.39
1.03 (0.86–1.22)	1.04 (0.87–1.24)	1.10 (0.93–1.30)	1.62 (1.32–1.98)	<0.001	
1.09 (0.97–1.23)	1.13 (1.01–1.28)	1.21 (1.08–1.35)	1.66 (1.43–1.92)	<0.001	
					<0.001
1.06 (0.91–1.23)	1.21 (1.05–1.40)	1.12 (0.97–1.29)	1.38 (1.14–1.68)	0.002	
1.15 (0.92–1.43)	1.24 (1.01–1.54)	1.31 (1.07–1.61)	2.27 (1.78–2.90)	<0.001	
1.29 (0.80–2.09)	0.83 (0.48–1.44)	1.18 (0.73–1.91)	1.57 (0.83–2.95)	<0.001	
1.13 (0.87–1.46)	0.95 (0.72–1.26)	1.35 (1.05–1.73)	1.79 (1.30–2.46)	<0.001	

¶ Multivariable adjusted models were based on the crude model with additional adjustment for smoking status (never smoked, former smoker [stopped ≥10 or <10 years ago or time since stopping unknown], current smoker [<15, 15 to 24, or ≥25 cigarettes per day or number unknown], or data missing), educational level (no school degree, primary-school degree, technical- or professional-school degree, secondary-school degree, university degree, or data missing), alcohol consumption (none, 0.1 to 4.9, 5.0 to 14.9, 15.0 to 29.9, or ≥30 g per day), activity (inactive, moderately inactive, moderately active, active, or data missing), and height (in quintiles). All covariates were entered into the models with the use of dummy coding.

‖ Relative risks in strata of smoking status were not adjusted for smoking status.

** Follow-up of 5 years or less indicates that follow-up time for all participants was censored after 5 years (i.e., only deaths occurring during the first 5 years were considered). Follow-up of more than 5 years indicates that person-time and incident events from the first 5 years of follow-up were excluded (i.e., only deaths that occurred after more than 5 years of follow-up were included).

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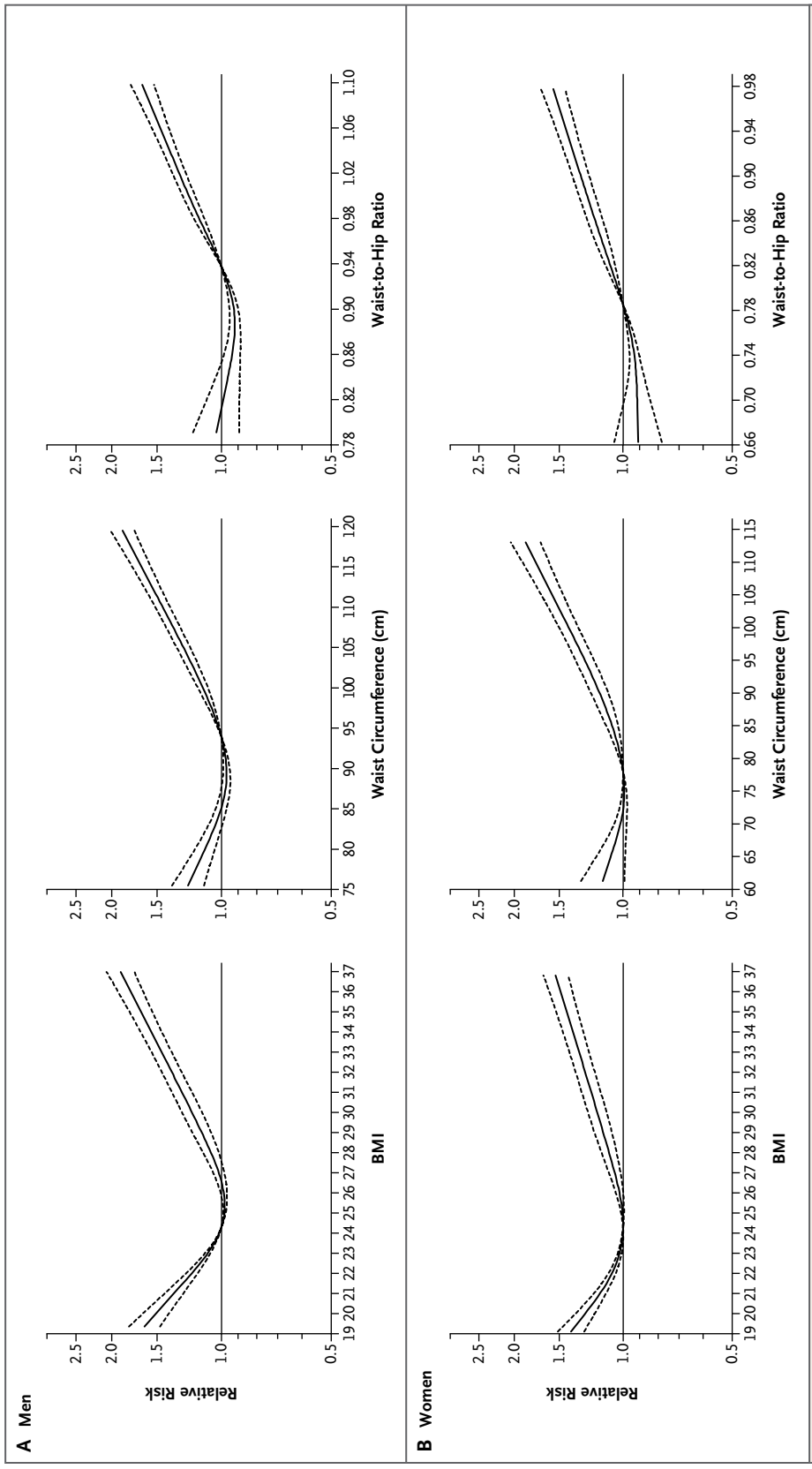

Figure 1. Adjusted Relative Risk of Death among Men and Women in the European Prospective Investigation into Cancer and Nutrition, According to BMI, Waist Circumference, and Waist-to-Hip Ratio.

The relative risk of death in association with body-mass index (BMI, the weight in kilograms divided by the square of the height in meters), waist circumference, and waist-to-hip ratio is shown in Panel A for men and in Panel B for women. Solid lines indicate relative risks, and dashed lines indicate 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 25th, 75th, and 95th percentiles of the sex-specific distribution of each anthropometric variable. The reference point for BMI is the midpoint of the reference group (23.5 to <25.0) from categorical analysis. The reference points for waist circumference and waist-to-hip ratio are the sex-specific medians of these variables. The graphs are truncated at the 1st and 99th percentiles. Age was used as the underlying time variable in the regression models, with stratification according to center and age at recruitment and additional adjustment for smoking status, educational level, alcohol consumption, physical activity, and height. The relative risks are plotted on a logarithmic scale.

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associations were slightly but significantly stronger among men than among women (P=0.001 for an interaction). When not adjusted for BMI, waist circumference and waist-to-hip ratio were significantly associated with the risk of death, with patterns similar to those observed for BMI (Fig. 1 and Table 2, and Table 3 in the Supplementary Appendix).

After further adjustment for BMI, waist circumference and waist-to-hip ratio showed a strong positive association with the risk of death (Table 2 and Fig. 2, and Table 3 in the Supplementary Appendix). For a given BMI in men and women, a waist circumference that was 5 cm larger was associated with a risk of death that was increased by a factor of 1.17 (95% confidence interval [CI], 1.15 to 1.20) among men and by a factor of 1.13 (95% CI, 1.11 to 1.15) among women (P=0.24 for the difference between men and women), and a waist-to-hip ratio that was 0.1 unit higher was associated with a risk that was increased by a factor of 1.34 (95% CI, 1.28 to 1.39) among men and by a factor of 1.24 (95% CI, 1.20 to 1.29) among women (P=0.04 for the difference between men and women). In models that included waist circumference or waist-to-hip ratio, BMI remained significantly associated with the risk of death (P<0.001). Hip circumference was not significantly associated with the risk of death after adjustment for BMI (data not shown).

The associations of waist circumference and waist-to-hip ratio with the risk of death tended to be stronger among participants with a lower BMI, as compared with those who had a higher BMI (Table 2, and Table 3 in the Supplementary Appendix). On cross-classification, participants in the lowest third of BMI and the highest quintile of waist circumference or waist-to-hip ratio, as compared with the reference group (participants in the middle third of BMI and the lowest quintile of waist circumference or waist-to-hip ratio), had the highest relative risk of death (Fig. 3). The findings were similar when BMI was instead categorized as 18.5 to less than 25.0, 25.0 to less than 30.0, and 30.0 or greater (Fig. 1 in the Supplementary Appendix), although the ability to estimate relative risk precisely for the cross-classification of waist circumference by BMI was limited. Among men and women of normal weight, the relative risks in the highest quintile of waist circumference as compared with the lowest quintile were 2.06 (95% CI, 1.32 to 3.20; P<0.001 for trend) and 1.79 (95% CI, 1.39 to 2.31; P<0.001 for trend), respectively, and the relative risks in the highest quintile of waist-to-hip ratio as compared with the lowest quintile were 1.79 (95% CI, 1.53 to 2.10; P<0.001 for trend) and 1.53 (95% CI, 1.34 to 1.75; P<0.001 for trend), respectively.

The addition of waist circumference or waist-to-hip ratio to the regression model that included BMI slightly but significantly increased the C statistic (Table 4 in the Supplementary Appendix). As shown in Table 3, and in Table 5 in the Supplementary Appendix, despite general agreement among the three regression models across the subject classifications (kappa values, 0.83 to 0.87), predicted risk categories changed substantially, and the model estimated the 5-year risk of death more accurately with the addition of waist circumference or waist-to-hip ratio than without these variables for men who had an absolute risk of 2.5% or greater and for women who had a risk of 1.25% or greater. The net reclassification index (which indicates the correct movement of participants across predefined risk categories, and thus depends on the choice of risk categories[31]) was significant only for the addition of waist-to-hip ratio to BMI among women. However, the integrated discrimination index (which does not depend on the choice of risk categories[31]) was highly significant for the addition of waist circumference or waist-to-hip ratio to BMI among participants of both sexes (Table 4 in the Supplementary Appendix).

SUBGROUP ANALYSES

In subgroup analyses, the relative risk of death associated with a high BMI as compared with reference BMI levels was higher among participants who had never smoked than among former or current smokers, whereas the relative risk at low as compared with reference BMI levels was higher among former and current smokers (Table 1). Among participants who had never smoked, the risk of death was lowest at a BMI of 24.5 for men and 23.9 for women (Fig. 2 and 3 in the Supplementary Appendix). Associations of waist circumference and waist-to-hip ratio with the risk of death tended to be slightly stronger among current smokers than among those who had never smoked, although the test for an interaction was significant for waist circumference only among men (Table 2, and Table 3 in the Supplementary Appendix). When participants were cross-

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Table 2. Relative Risk of Death According to Quintiles of Waist Circumference among Men and Women.*

Relative Risk	Quintile of Waist Circumference					P Value for Trend†	P Value for Interaction‡
	1	2	3	4	5		
Men							
Waist circumference (cm)	<86.0	86.0 to <91.5	91.5 to <96.5	96.5 to <102.7	≥102.7		
Deaths (no.)	1242	1250	1392	1629	2259		
Overall relative risk (95% CI)							
Crude§	1.00	0.88 (0.81–0.95)	0.91 (0.84–0.98)	1.01 (0.93–1.09)	1.35 (1.26–1.46)	<0.001	
Adjusted¶							
Without BMI	1.00	0.91 (0.84–0.98)	0.94 (0.87–1.02)	1.05 (0.97–1.13)	1.33 (1.24–1.44)	<0.001	
With BMI	1.00	1.15 (1.05–1.26)	1.35 (1.22–1.50)	1.63 (1.46–1.83)	2.05 (1.80–2.33)	<0.001	
Relative risk by subgroup (95% CI)¶							
BMI thirds							0.03
<24.9	1.00	1.19 (1.07–1.32)	1.46 (1.28–1.67)	1.64 (1.34–2.00)	2.51 (1.59–3.96)	<0.001	
24.9 to <27.7	1.00	1.16 (0.92–1.47)	1.37 (1.09–1.71)	1.73 (1.37–2.19)	2.01 (1.54–2.63)	<0.001	
≥27.7	1.00	0.67 (0.33–1.36)	0.53 (0.28–1.02)	0.68 (0.36–1.30)	0.87 (0.46–1.66)	<0.001	
Smoking status‖							0.02
Never smoked	1.00	1.03 (0.84–1.26)	1.23 (0.98–1.54)	1.39 (1.08–1.80)	1.71 (1.28–2.30)	<0.001	
Former smoker	1.00	1.26 (1.07–1.48)	1.46 (1.22–1.75)	1.78 (1.46–2.15)	2.54 (2.05–3.16)	<0.001	
Current smoker	1.00	1.20 (1.05–1.37)	1.42 (1.22–1.65)	1.81 (1.53–2.15)	2.24 (1.83–2.73)	<0.001	
Age							0.05
<55 yr	1.00	1.20 (1.01–1.42)	1.26 (1.04–1.53)	1.60 (1.28–1.98)	1.99 (1.55–2.57)	<0.001	
55 to <65 yr	1.00	1.10 (0.96–1.26)	1.35 (1.16–1.57)	1.62 (1.37–1.91)	2.22 (1.83–2.68)	<0.001	
≥65 yr	1.00	1.22 (1.02–1.45)	1.44 (1.18–1.75)	1.64 (1.33–2.04)	1.78 (1.39–2.27)	<0.001	
Follow-up**							0.10
≤5 yr	1.00	1.10 (0.94–1.28)	1.43 (1.21–1.69)	1.63 (1.35–1.96)	1.87 (1.51–2.31)	<0.001	
>5 yr	1.00	1.19 (1.06–1.33)	1.31 (1.15–1.49)	1.63 (1.42–1.88)	2.15 (1.83–2.53)	<0.001	
Cause of death							0.01
Cancer	1.00	1.16 (0.99–1.35)	1.37 (1.15–1.63)	1.51 (1.25–1.83)	1.89 (1.51–2.36)	<0.001	
Circulatory	1.00	1.22 (1.02–1.47)	1.36 (1.11–1.67)	1.59 (1.27–1.99)	1.81 (1.40–2.33)	<0.001	
Respiratory	1.00	1.38 (0.91–2.11)	2.14 (1.33–3.45)	3.37 (1.99–5.71)	6.56 (3.60–11.96)	<0.001	
Other	1.00	1.03 (0.82–1.29)	1.48 (1.15–1.90)	1.68 (1.27–2.23)	2.38 (1.72–3.30)	<0.001	

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Women							
Waist circumference (cm)	<70.1	70.1 to <75.6	75.6 to <81.0	81.0 to <89.0	≥89.0		
Deaths (no.)	913	1107	1308	1569	1973		
Overall relative risk (95% CI)							
Crude§	1.00	0.96 (0.88–1.05)	0.93 (0.86–1.02)	1.06 (0.97–1.15)	1.33 (1.22–1.44)	<0.001	
Adjusted¶							
Without BMI	1.00	0.97 (0.89–1.07)	0.93 (0.85–1.01)	1.05 (0.96–1.14)	1.28 (1.17–1.39)	<0.001	
With BMI	1.00	1.16 (1.05–1.28)	1.21 (1.09–1.35)	1.46 (1.30–1.64)	1.78 (1.56–2.04)	<0.001	
Relative risk by subgroup (95% CI)¶							
BMI thirds							0.03
<23.0	1.00	1.17 (1.04–1.31)	1.27 (1.10–1.47)	1.70 (1.36–2.13)	2.87 (1.91–4.32)	<0.001	
23.0 to <26.6	1.00	0.98 (0.80–1.21)	0.95 (0.77–1.17)	1.12 (0.90–1.39)	1.48 (1.14–1.92)	<0.001	
≥26.6	1.00	0.87 (0.37–2.08)	1.24 (0.56–2.74)	1.45 (0.66–3.17)	1.74 (0.79–3.81)	<0.001	
Smoking status‖							0.18
Never smoked	1.00	1.03 (0.88–1.20)	1.13 (0.96–1.33)	1.40 (1.17–1.67)	1.64 (1.34–2.01)	<0.001	
Former smoker	1.00	1.35 (1.10–1.66)	1.27 (1.02–1.59)	1.62 (1.27–2.07)	1.96 (1.48–2.60)	<0.001	
Current smoker	1.00	1.28 (1.08–1.51)	1.43 (1.18–1.73)	1.66 (1.34–2.06)	2.36 (1.83–3.03)	<0.001	
Age							0.75
<55 yr	1.00	1.14 (0.97–1.34)	1.12 (0.93–1.35)	1.26 (1.01–1.56)	1.66 (1.28–2.14)	<0.001	
55 to <65 yr	1.00	1.16 (0.99–1.35)	1.34 (1.13–1.58)	1.57 (1.30–1.89)	1.91 (1.55–2.36)	<0.001	
≥65 yr	1.00	1.19 (0.97–1.46)	1.13 (0.91–1.40)	1.51 (1.20–1.90)	1.75 (1.36–2.27)	<0.001	
Follow-up**							0.67
≤5 yr	1.00	1.26 (1.05–1.50)	1.23 (1.01–1.49)	1.49 (1.21–1.85)	1.91 (1.50–2.43)	<0.001	
>5 yr	1.00	1.12 (1.00–1.26)	1.21 (1.07–1.38)	1.45 (1.26–1.67)	1.72 (1.46–2.03)	<0.001	
Cause of death							0.01
Cancer	1.00	1.11 (0.96–1.28)	1.07 (0.91–1.26)	1.24 (1.04–1.49)	1.30 (1.05–1.60)	0.01	
Circulatory	1.00	1.28 (1.00–1.64)	1.29 (0.99–1.68)	1.71 (1.29–2.27)	2.31 (1.69–3.16)	<0.001	
Respiratory	1.00	1.16 (0.70–1.90)	1.76 (1.05–2.94)	2.29 (1.29–4.07)	2.95 (1.52–5.70)	<0.001	
Other	1.00	1.34 (1.04–1.73)	1.61 (1.22–2.13)	1.92 (1.40–2.63)	2.72 (1.90–3.90)	<0.001	

* BMI denotes body-mass index, which is the weight in kilograms divided by the square of the height in meters. CI denotes confidence interval.

† P values are based on median waist circumference within quintiles.

‡ P values, calculated with the use of the likelihood-ratio test, are for comparisons of the model that included interaction terms between waist circumference and the stratification variable with the model that did not include these interaction terms (with 8 degrees of freedom each for BMI, smoking status, and age, 12 degrees of freedom for cause of death, and 4 degrees of freedom for length of follow-up); for cause of death and length of follow-up, the data augmentation method described by Lunn and McNeil was used.[26]

§ The crude relative risk was calculated with the use of Cox proportional-hazards regression, with age as the underlying time variable and stratification according to center and age at recruitment.

¶ Multivariable adjusted models were based on the crude model with additional adjustment for smoking status (never smoked, former smoker [stopped ≥10 or <10 years ago or time since stopping unknown], current smoker [<15, 15 to 24, or ≥25 cigarettes per day or number unknown], or data missing), educational level (no school degree, primary-school degree, technical- or professional-school degree, secondary-school degree, university degree, or data missing), alcohol consumption (none, 0.1 to 4.9, 5.0 to 14.9, 15.0 to 29.9, or ≥30 g per day), activity (inactive, moderately inactive, moderately active, active, or data missing), height (in quintiles), and BMI (<18.5, 18.5 to <21.0, 21.0 to <23.5, 23.5 to <25.0, 25.0 to <26.5, 26.5 to <28.0, 28.0 to <30.0, 30.0 to <35.0, or ≥35.0).

‖ Relative risks in strata of smoking status are not adjusted for smoking status.

** Follow-up of 5 years or less indicates that the follow-up time of all participants was censored after 5 years (i.e., only deaths occurring during the first 5 years are considered). Follow-up of longer than 5 years indicates that person-time and incident events from the first 5 years of follow-up were excluded (i.e., that analysis includes only the deaths that occurred after more than 5 years of follow-up).

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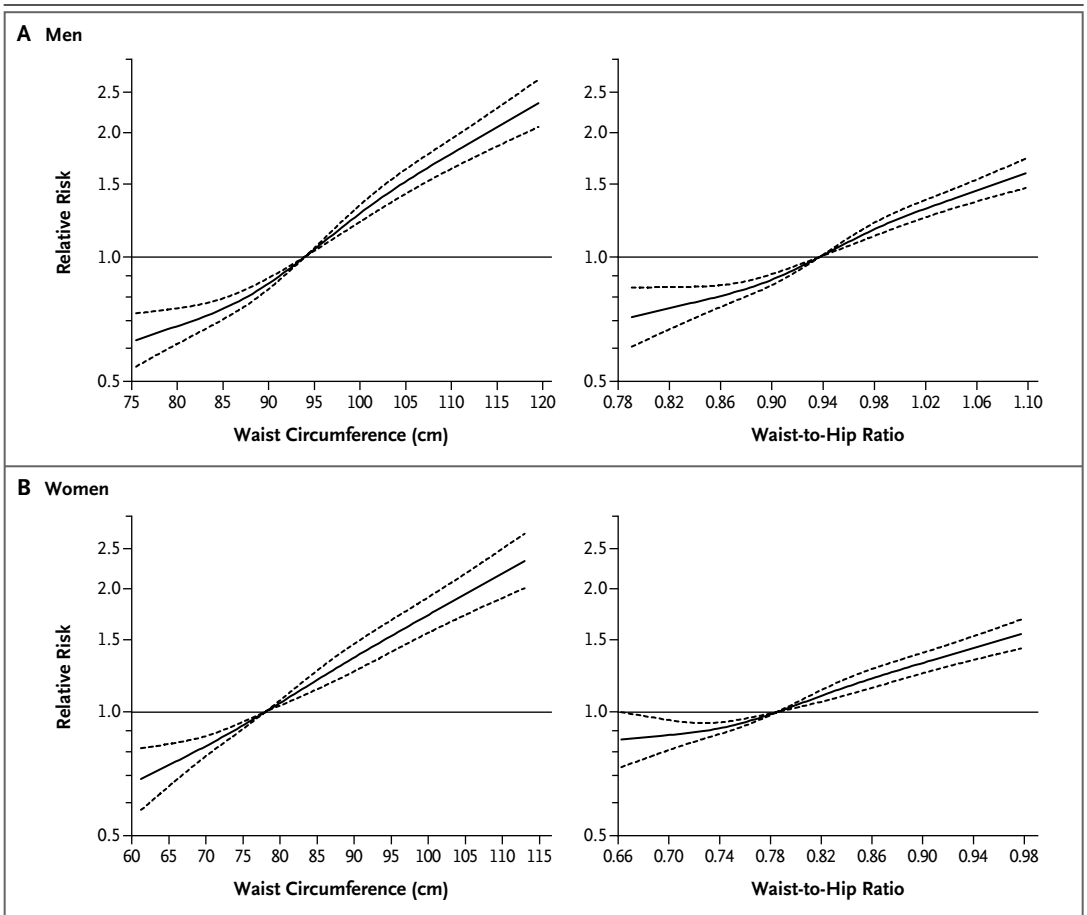

Figure 2. Adjusted Relative Risk of Death among Men and Women, According to Waist Circumference and Waist-to-Hip Ratio after Adjustment for BMI.

The relative risk of death in association with waist circumference and waist-to-hip ratio, after adjustment for BMI, is shown in Panel A for men and in Panel B for women. Solid lines indicate relative risks, and dashed lines indicate 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 25th, 75th, and 95th percentiles of the sex-specific distribution of each anthropometric variable. The reference points for waist circumference and waist-to-hip ratio are the sex-specific medians of these variables. The graphs are truncated at the 1st and 99th percentiles. Age was used as the underlying time variable in the regression models, with stratification by center and age at recruitment and additional adjustment for smoking status, educational level, alcohol consumption, physical activity, height, and BMI. The relative risks are plotted on a logarithmic scale.

classified, the associations within the group of participants who had never smoked were similar to those reported for the entire cohort (Fig. 4 in the Supplementary Appendix). The association of a high BMI with an increased risk of death was stronger among younger men than among older men, and the association of general and abdominal adiposity with the risk of death among men tended to be stronger for deaths occurring more than 5 years after enrollment than for deaths occurring earlier. The relative risks of death associated with a high BMI were strongest for circulatory causes of death, followed by other causes and neoplasms, whereas the relative risks associated with a high waist circumference or waist-to-hip ratio were strongest for respiratory causes of death, followed by other causes (Tables 1 and 2; and Tables 3, 6, 7, and 8 and Fig. 5 in the Supplementary Appendix).

We observed significant heterogeneity across centers among men but not among women for the association of BMI and of waist circumference with the risk of death ($P=0.001$ for BMI and $P=0.004$ for waist circumference). This heterogeneity was driven primarily by the center in Greece, in which associations were weaker than those for

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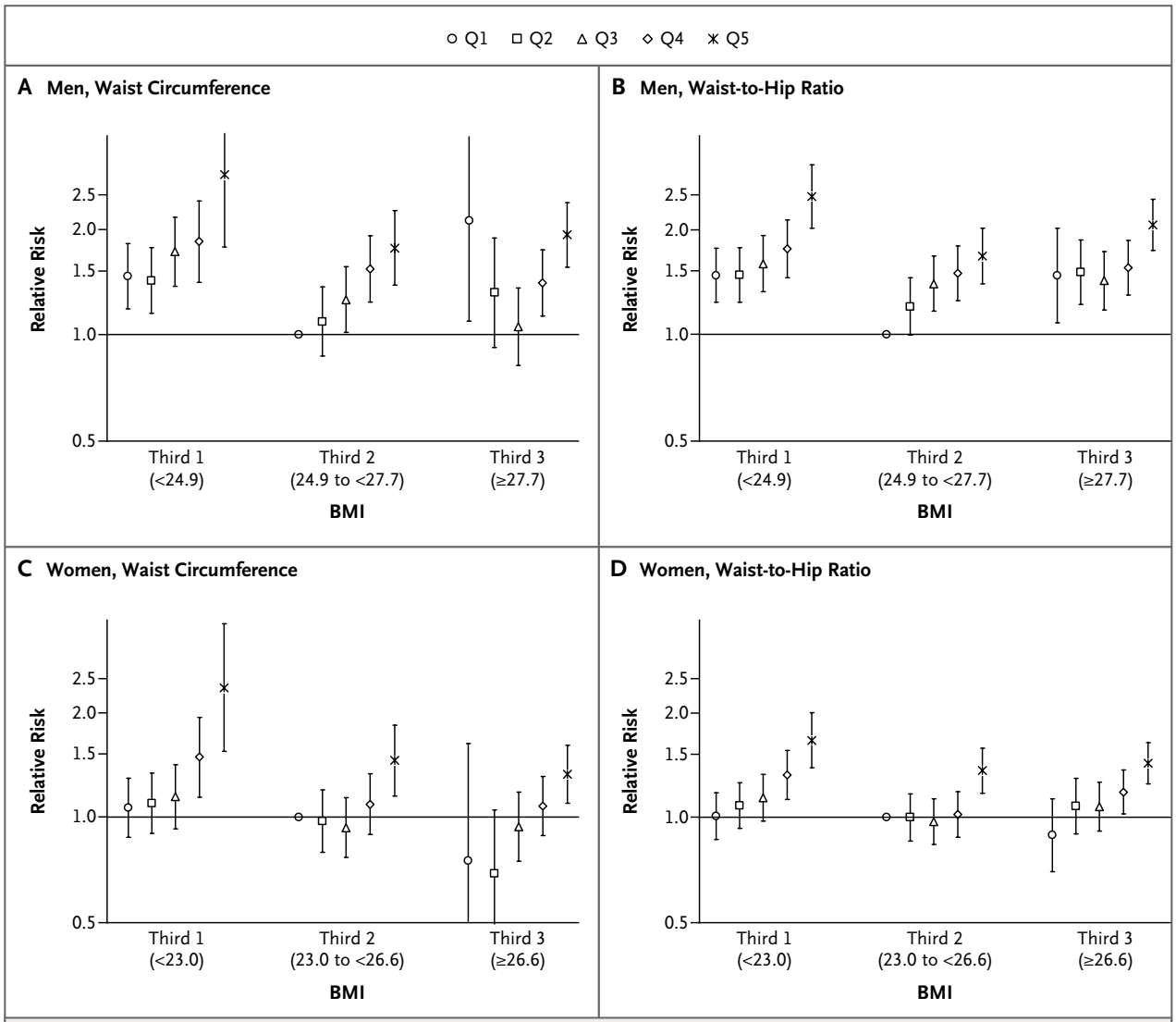

Figure 3. Adjusted Relative Risk of Death among Men and Women According to Thirds of BMI and Quintiles of Waist Circumference or Waist-to-Hip Ratio.

The relative risk of death according to thirds of BMI and according to quintiles of waist circumference and waist-to-hip ratio is shown in Panels A and B, respectively, for men and in Panels C and D, respectively, for women. The reference category consists of participants in the middle third of BMI and the bottom quintile of waist circumference or waist-to-hip ratio. Age was used as the underlying time variable in the regression models, with stratification according to center and age at recruitment and additional adjustment for smoking status, educational level, alcohol consumption, physical activity, and height. T or I bars indicate 95% confidence intervals for the relative risk of death. In Panel A, the upper boundary of the 95% confidence interval for men in the lowest third of BMI and the highest quintile of waist circumference was 4.60, and the upper boundary of the 95% confidence interval for men in the highest third of BMI and the lowest quintile of waist circumference was 4.07. In Panel C, the lower boundary of the 95% confidence interval for women in the highest third of BMI and the lowest quintile of waist circumference was 0.35, and the lower boundary of the 95% confidence interval for women in the highest third of BMI and the second quintile of waist circumference was 0.45. The relative risks are plotted on a logarithmic scale. Q denotes quintile.

the overall cohort. When the Greek center was excluded, the tests for heterogeneity were no longer significant (P>0.05), but the overall estimates of relative risk did not change substantially. When we performed sensitivity analyses in which we added the EPIC participants who had been excluded from our main study because their anthropometric measures were based only on self-report, the overall relative risks did not change appreciably.

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Table 3. Expected and Observed 5-Year Risk of Death According to the Adjusted Model, with and without Waist Circumference.*

5-Year Risk According to Model with BMI	5-Year Risk According to Model with BMI and Waist Circumference				Total Reclassified
Men	**<2.5%**	**2.5 to <5.0%**	**5.0 to <7.5%**	**≥7.5%**	
<2.5%					
Total participants (no.)	86,057	1,812	0	0	
Participants classified in each stratum according to model with BMI and waist circumference (%)	97.94	2.06	0	0	2.06
Observed 5-yr risk (%)	0.92	2.37	—	—	
2.5 to <5.0%					
Total participants (no.)	1,943	17,403	950	1	
Participants classified in each stratum according to model with BMI and waist circumference (%)	9.57	85.74	4.68	0	14.25
Observed 5-yr risk (%)	2.16	3.49	5.47	0	
5.0 to <7.5%					
Total participants (no.)	0	892	4,998	577	
Participants classified in each stratum according to model with BMI and waist circumference (%)	0	13.79	77.28	8.92	22.71
Observed 5-yr risk (%)	—	4.71	6.98	7.80	
≥7.5%					
Total participants (no.)	0	2	563	5,640	
Participants classified in each stratum according to model with BMI and waist circumference (%)	0	0.03	9.07	90.89	9.10
Observed 5-yr risk (%)	—	0	7.82	14.22	
Women	**<1.25%**	**1.25 to <2.50%**	**2.50 to <3.75%**	**≥3.75%**	
<1.25%					
Total participants (no.)	179,814	3,227	0	0	
Participants classified in each stratum according to model with BMI and waist circumference (%)	98.24	1.76	0	0	1.76
Observed 5-yr risk (%)	0.41	1.46	—	—	
1.25 to <2.50%					
Total participants (no.)	2,933	25,996	1,497	6	
Participants classified in each stratum according to model with BMI and waist circumference (%)	9.64	85.42	4.92	0.02	14.58
Observed 5-yr risk (%)	1.23	1.74	2.00	0	
2.50 to <3.75%					
Total participants (no.)	0	1,457	7,053	898	
Participants classified in each stratum according to model with BMI and waist circumference (%)	0	15.49	74.97	9.55	25.04
Observed 5-yr risk (%)	—	1.85	2.91	3.67	
≥3.75%					
Total participants (no.)	0	4	864	8,334	
Participants classified in each stratum according to model with BMI and waist circumference (%)	0	0.04	9.39	90.57	9.43
Observed 5-yr risk (%)	—	0	3.36	6.89	

* The multivariable logistic model included age (in 5-year categories), center, smoking status (never smoked, former smoker [stopped ≥10 or <10 years ago or time since stopping unknown], current smoker [<15, 15 to 24, or ≥25 cigarettes per day or number unknown], or data missing), educational level (no school degree, primary-school degree, technical- or professional-school degree, secondary-school degree, university degree, or data missing) alcohol consumption (none, 0.1 to 4.9, 5.0 to 14.9, 15.0 to 29.9, or ≥30 g per day), activity (inactive, moderately inactive, moderately active, active, or data missing), height (in quintiles), and BMI (<18.5, 18.5 to <21.0, 21.0 to <23.5, 23.5 to <25.0, 25.0 to <26.5, 26.5 to <28.0, 28.0 to <30.0, 30.0 to <35.0, or ≥35.0).

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DISCUSSION

In this large European cohort study, general and abdominal adiposity were independently related to the risk of death. The associations of BMI with the risk of death were J-shaped, with higher risks of death observed in the lower and upper BMI categories than in the middle categories. In contrast, once general adiposity was adjusted for, abdominal fat distribution was positively associated with the risk of death. These associations tended to be stronger among participants with a lower BMI than among those with a higher BMI. Thus, measurement of both general and abdominal adiposity provides a better assessment of the risk of death, particularly among people with a lower BMI.

The most appropriate adiposity markers for assessing the risk of disease and death are debated.[4,32] Waist circumference and BMI are highly correlated and when considered individually reflect the extent of both abdominal and general obesity. However, the large sample in our study enabled us to estimate with sufficient precision the effect of abdominal adiposity on the risk of death independently of general obesity. The waist-to-hip ratio is less strongly related to BMI than is waist circumference and is therefore a more specific surrogate for fat distribution. Although the waist-to-hip ratio may therefore be preferred as a predictor of the risk of death, in addition to BMI, because it has less potential for collinearity, the use of waist circumference has been predominantly proposed in the past decade, largely because waist circumference is easier to measure and to interpret than the waist-to-hip ratio.[2,33]

The current results underscore the importance of assessing the distribution of body fat even among persons of normal weight and challenge the use of cutoff points to define abdominal obesity, at least when they are used to predict the risk of death.[2,34] Our finding of a positive association between waist circumference and the risk of death among participants of normal weight may also explain why studies have been unable to show a linear relationship between BMI and the risk of death across the entire range of BMI values.

Like previous studies, our study showed that general obesity was more strongly related to the risk of death among participants who had never smoked, whereas underweight was more strongly related to the risk of death among current smokers; these results may reflect the finding that smokers have a lower body weight but a higher risk of death than nonsmokers.[15,17,35] In contrast, after adjustment for BMI, the association of waist circumference with the risk of death was stronger among smokers. Smokers tend to have a metabolically more adverse fat-distribution profile, with higher central adiposity, than nonsmokers.[36] Older persons may be more likely than younger persons to have underlying but undiagnosed chronic diseases that are related to a lower BMI and an increased risk of death. Obesity appeared to be more strongly related to the risk of death among younger men than among older men, whereas no such difference was observed among women. The reasons for these sex differences are unclear and may reflect biologic factors or the play of chance. It is also important to note that the absolute risk of death in the reference category varied across subgroups. For example, although general adiposity was more strongly related to the risk of death among people who had never smoked than among current smokers, the absolute risk of death was higher among current smokers (data not shown).

Adipose tissue, particularly tissue from visceral-fat deposits, secretes potential mediators in the development of chronic diseases[1]; this process may explain why abdominal fat distribution was related to the risk of death independently of BMI. Body mass is more closely related to the amount of visceral fat in men than in women,[37] which may be among the reasons that the relative risk of death among participants with a high BMI was higher for men than for women. The increased risk of death among participants with a low BMI could be the result of low muscle mass, since even at a low BMI, waist circumference was positively related to the risk of death. As in the present study, a recent report suggested that the increase in the risk of death associated with a low BMI is driven primarily by respiratory and other causes, whereas the increased risk associated with a high BMI is driven by cardiovascular causes and cancer.[18] Although abdominal adiposity is related to chronic inflammation, which may lead to the development of chronic bronchitis and other diseases, the mechanisms for the strong positive associations with deaths from respiratory and other causes are unclear.[38]

Our study has certain limitations. Although people who had a history of cancer, heart dis-

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ease, or stroke were excluded, our analysis may have included a number of participants who had other serious diseases that could potentially confound the observed associations. Nevertheless, we believe that the number of participants with other serious diseases at baseline was small because it is unlikely that such persons would decide to participate in a long-term cohort study. This assumption is indirectly supported by the low prevalence of cancer, heart disease, and stroke in the original EPIC study population. The association of adiposity with the risk of death may vary with a longer follow-up period; however, it would probably become stronger, as suggested by our sensitivity analysis.

The improvement in the prediction of risk by the addition of waist circumference or waist-to-hip ratio to BMI was small with respect to the C statistic, as would be expected, since the C statistic is very insensitive to the detection of true predictors.[30,39] In contrast, and clinically more important,[30] the addition of waist circumference or waist-to-hip ratio to BMI more accurately stratified participants into higher-risk and lower-risk categories.

The causes of heterogeneity across centers, driven by the Greek cohort, are unclear and may reflect differences in the way in which anthropometric measurements were performed, biologic diversity among different populations, or the play of chance. Nevertheless, the relative-risk estimates for the overall cohort did not change substantially when the participants from Greece were excluded from the analysis.

The use of overall mortality and broad categories of cause-specific mortality in our analysis of risk may limit interpretations of the causes of the associations. Nevertheless, such research is crucial for estimating whether reductions in the prevalence of adiposity would affect a population's mortality. Although the level of accuracy for the coding of deaths from cancer and circulatory causes on the basis of information from death certificates is high, it may be lower for the coding of deaths from respiratory causes.[40] Therefore, the analyses according to the cause of death have to be interpreted cautiously. In addition, imperfect follow-up procedures may have resulted in the erroneous classification of some deceased participants as alive. However, we believe that this number was negligibly small, and, given the large sample, the reduction in sensitivity would have no substantial effect on the estimates of relative risk. Finally, although we adjusted our analyses for several variables, because of the observational nature of the study, we cannot exclude the possibility of residual confounding.

In conclusion, the findings of our study suggest that general and abdominal adiposity are both associated with the risk of death. The results support the use of waist circumference or waist-to-hip ratio in addition to BMI in the assessment of the risk of death, particularly among persons with a low BMI.

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APPENDIX

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