American Journal of Epidemiology

Vol. 174, No. 1
DOI: 10.1093/aje/kwr048
Advance Access publication:
May 26, 2011

Original Contribution

Associations Between General and Abdominal Adiposity and Mortality in Individuals With Diabetes Mellitus

Diewertje Sluik*, Heiner Boeing, Jukka Montonen, Tobias Pischon, Rudolf Kaaks, Birgit Teucher, Anne Tjønneland, Jytte Halkjaer, Tina L. Berentzen, Kim Overvad, Larraitz Arriola, Eva Ardanaz, Benedetta Bendinelli, Sara Grioni, Rosario Tumino, Carlotta Sacerdote, Amalia Mattiello, Annemieke M. W. Spijkerman, Daphne L. van der A, Joline W. Beulens, Yvonne T. van der Schouw, Peter M. Nilsson, Bo Hedblad, Olov Rolandsson, Paul W. Franks, and Ute Nöthlings

* Correspondence to Diewertje Sluik, Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Arthur-Scheunert-Allee 114–116, 14558 Nuthetal, Germany (e-mail: diewertje.sluik@dife.de).

Initially submitted October 13, 2010; accepted for publication February 8, 2011.

Individuals with diabetes mellitus are advised to achieve a healthy weight to prevent complications. However, fat mass distribution has hardly been investigated as a risk factor for diabetes complications. The authors studied associations between body mass index, waist circumference, waist/hip ratio, and waist/height ratio and mortality among individuals with diabetes mellitus. Within the European Prospective Investigation into Cancer and Nutrition, a subcohort was defined as 5,435 individuals with a confirmed self-report of diabetes mellitus at baseline in 1992–2000. Participants were aged 57.3 (standard deviation, 6.3) years, 54% were men, the median diabetes duration was 4.6 (interquartile range, 2.0–9.8) years, and 22% of the participants used insulin. Body mass index, as indicator of general obesity, was not associated with higher mortality, whereas all measurements of abdominal obesity showed a positive association. Associations generally were slightly weaker in women. The strongest association was observed for waist/height ratio: In the fifth quintile, the hazard rate ratio was 1.88 (95% confidence interval: 1.33, 2.65) for men and 2.46 (95% confidence interval: 1.46, 4.14) for women. Measurements of abdominal, but not general, adiposity were associated with higher mortality in diabetic individuals. The waist/height ratio showed the strongest association. Respective indicators might be investigated in risk prediction models.

adiposity; body mass index; diabetes complications; diabetes mellitus; mortality; waist circumference; waist-hip ratio

Abbreviations: CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRR, hazard rate ratio; ICD-10, *International Statistical Classification of Diseases, Injuries, and Causes of Death*, Tenth Revision.

Individuals with diabetes mellitus have a high risk of experiencing severe complications such as cardiovascular diseases (1). It has been estimated that as many as 80% of the patients will experience macrovascular complications (2), and individuals with diabetes have a 2-fold higher risk of myocardial infarction and stroke than those without (3). The high risk of cardiovascular complications goes along with a higher overall mortality (4) and mortality due to cancers (5). Diabetes management focuses on the prevention of these late complications (2).

The major recommendation for nutrition and lifestyle therapy of diabetes type 2 is weight loss for the overweight and obese (6). In the general population, general and abdominal obesity has been associated with increased risk of mortality (7, 8). However, studies on obesity and mortality among individuals with diabetes have yielded inconsistent results. The association between body mass index and mortality in individuals with diabetes has been reported as favorable (9–12), detrimental (10, 13–15), or U- or J-shaped (16, 17), or no association has been observed (18, 19). However, studies have been heterogeneous in size and quality. All studies except 2 (20, 21) focused on body mass index as an indicator of obesity and did not take body fat distribution as reflected by measures of abdominal adiposity into account.

The objective of the present study was to investigate the associations of general adiposity as measured by body mass index and abdominal adiposity, as measured by waist circumference, waist/hip ratio, and waist/height ratio (22), with overall and cause-specific mortality in a European diabetic population.

MATERIALS AND METHODS

Study design

This study was nested within the European Prospective Investigation into Cancer and Nutrition (EPIC). EPIC is an ongoing cohort study of 519,978 men and women from 10 European countries (23). Participants were aged 35–70 years at enrollment between 1992 and 2000 and were recruited predominantly from the general population residing in a given geographic area. Participants signed informed consent forms, and study approval was obtained from the ethical review boards of the International Agency for Research on Cancer and review boards at the local study centers.

For the current study, 15 study centers from 6 countries provided additional data on diabetes diagnosis and medication (Denmark: Aarhus, Copenhagen; Germany: Heidelberg, Potsdam; Italy: Florence, Milan, Naples, Ragusa, Turin; the Netherlands: Bilthoven, Utrecht; Spain: Pamplona, San Sebastian; Sweden: Malmö, Umea). A subcohort of participants with a confirmed diagnosis of diabetes mellitus at study entry was defined. Self-reports obtained at baseline were confirmed by additional information sources, which varied by study center and include the following: contact with a medical practitioner, self-reported use of diabetes-related medication (e.g., insulin or blood glucose-lowering drugs), repeated self-report during follow-up, linkage to diabetes registries, or a glycated hemoglobin level above 6% (Malmö only).

Study population

Of the initial 7,048 self-reports in the participating EPIC centers, 5,542 participants were confirmed to have had diabetes at baseline. Subsequently, 870 additional cases were included because they turned out to have been prevalent diabetes cases when self-reports were verified for incident cases in conjunction with another study. This led to a subcohort comprising 6,412 individuals with confirmed diabetes at baseline. After exclusion of participants with missing baseline questionnaire data ($n = 6$), participants with missing dietary information ($n = 9$), participants in the highest and lowest 1% of the ratio of energy intake to estimated energy requirement ($n = 177$), deceased participants with missing date of death ($n = 1$), and participants with missing information on age at diabetes diagnosis ($n = 422$), body mass index ($n = 39$), or waist circumference ($n = 337$), which included the whole cohort of Umeå, the analytical sample comprised 5,435 participants.

Assessment of anthropometric data and other covariates

Following the EPIC study protocol, weight and height were measured with participants not wearing shoes. Waist circumference was measured at the narrowest circumference of the torso (Italy; Utrecht, the Netherlands; Heidelberg, Germany; Denmark; Spain) or at the midpoint between the lower ribs and iliac crest (Bilthoven, the Netherlands; Potsdam, Germany; Malmö, Sweden). It was not anticipated that differences in measurement methods would affect the results (24). Hip circumference was measured horizontally at the widest circumference of the hips (Italy; Spain; Bilthoven, the Netherlands; Malmö, Sweden) or over the buttocks (Utrecht, the Netherlands; Germany; Denmark). Because the amount of clothing worn during the measurement differed among study centers, each participant's body weight and waist and hip circumferences were corrected in order to reduce heterogeneity due to these protocol differences. For participants who were normally dressed and without shoes, 1.5 kg for weight and 2.0 cm for circumferences were subtracted from the original measurement (Utrecht, the Netherlands; Turin, Italy), while for participants in light clothing without shoes,1 kg was subtracted from weight (Bilthoven, the Netherlands; Malmö, Sweden). No corrections were made for the other study centers where participants wore light underwear only (8).

Further lifestyle- and health-related variables were collected by using questionnaires, with close to identical questions translated for the different countries. Questionnaires included questions on smoking history (i.e., smoking status, duration, intensity), educational level, physical activity, and medical history including prevalent heart disease and stroke. Baseline alcohol consumption was derived from a dietary questionnaire, which assessed intake during the previous 12 months. Duration since diabetes diagnosis was calculated by subtracting the age at the self-reported year of diagnosis or, when available, the exact date of diagnosis supplied by the medical practitioner from the age at baseline examination. Information on insulin use according to the Anatomical Therapeutic Chemical classification of the World Health Organization was either self-reported medication for treatment or obtained during medical verification.

Assessment of endpoints

Causes and dates of deaths were ascertained by using record linkages with local, regional, or central cancer registries, boards of health, or death indexes (Denmark, Italy, the Netherlands, Spain, Sweden). Germany identified deceased participants with follow-up mailings and subsequent inquiries to municipality registries, regional health departments, physicians, or hospitals. Mortality data were coded according to the *International Statistical Classification of Diseases, Injuries, and Causes of Death*, Tenth Revision (ICD-10). For the cause-specific analyses, deaths due to circulatory diseases (ICD-10 codes I00-I99), cancer (ICD-10 codes C00-D48), and all other known causes were grouped accordingly. Deaths where the specific cause was unavailable were not included in the cause-specific analysis.

Table 1. Baseline Characteristics[a] of Study Participants From the European Prospective Investigation Into Cancer and Nutrition With a Confirmed Diagnosis of Diabetes Mellitus at Baseline in 1992–2000 Within Sex-specific Quintiles of Body Mass Index

	Quintile of Body Mass Index																									
	1					2					3					4					5					P_{trend}[b]
	Mean (SD)	Median	IQR	No.	%	Mean (SD)	Median	IQR	No.	%	Mean (SD)	Median	IQR	No.	%	Mean (SD)	Median	IQR	No.	%	Mean (SD)	Median	IQR	No.	%	
											Men															
Body mass index, kg/m^2	23.1 (1.5)					26.1 (0.6)					28.1 (0.6)					30.4 (0.8)					34.8 (2.9)					<0.001
Age, years	56.4 (6.4)					57.6 (5.9)					57.4 (6.0)					57.1 (6.0)					58.6 (6.0)					0.79
Height, cm	174.6 (7.4)					173.0 (6.5)					173.5 (6.9)					172.7 (7.0)					172.7 (7.0)					<0.001
Waist circumference, cm	87.3 (6.3)					94.2 (5.2)					99.9 (5.3)					105.3 (5.3)					115.3 (8.4)					<0.001
Waist/hip ratio	0.92 (0.06)					0.96 (0.05)					0.98 (0.05)					1.00 (0.05)					1.02 (0.07)					<0.001
Waist/height ratio	0.50 (0.04)					0.55 (0.03)					0.58 (0.03)					0.61 (0.03)					0.67 (0.05)					<0.001
Alcohol intake, g/day		13	4–31				13	3–33				16	5–38				17	5–44				16	4–40			<0.001
Smoking status[c]																										
Never				159	27				140	24				134	23				134	23				130	22	0.05
Former				212	36				262	45				287	49				286	49				279	48	<0.001
Current				213	36				182	31				165	28				160	27				176	30	0.01
Physical activity[c]																										
Inactive				137	23				138	24				132	22				167	29				169	29	0.005
Moderately inactive				186	32				192	33				184	31				185	32				171	29	0.31
Moderately active				136	23				130	22				138	23				120	21				146	25	0.74
Active				123	21				125	21				123	21				105	18				98	17	0.02
Educational level[c]																										
None				21	4				16	3				28	5				35	6				22	4	0.17
Primary school				166	28				214	37				234	40				223	38				249	43	<0.001
Technical/professional school				147	25				153	26				139	24				149	26				159	27	0.53
Secondary school				74	13				63	11				54	9				37	6				41	7	<0.001
Longer (including university)				175	30				140	24				130	22				133	23				112	19	<0.001
History of myocardial infarction[c]				39	7				53	9				48	8				59	10				56	10	0.06
History of stroke[c]				19	3				25	4				29	5				20	4				18	3	0.64
History of cancer[c]				16	3				13	2				19	3				10	2				15	3	0.68
Age at diabetes, years		50	42–55				52	45–57				52	45–56				52	46–57				52	46–57			<0.001
Diabetes duration, years		5	2–11				5	2–10				5	2–10				4	2–9				3	1–7			<0.001
Insulin use				212	36				141	24				81	14				80	14				75	13	<0.001

	Women																				
Body mass index, kg/m^2	22.3 (1.8)				26.2 (0.8)				28.9 (0.8)				31.8 (0.9)				37.6 (3.7)				<0.001
Age, years	56.3 (7.4)				58.1 (6.2)				58.3 (6.3)				58.4 (6.1)				56.9 (6.4)				0.07
Height, cm	162.1 (6.6)				160.8 (6.9)				160.2 (6.2)				160.0 (6.5)				159.8 (6.8)				<0.001
Waist circumference, cm	76.1 (6.8)				85.5 (6.0)				91.9 (6.3)				98.5 (6.6)				109.3 (8.9)				<0.001
Waist/hip ratio	0.81 (0.06)				0.85 (0.06)				0.88 (0.06)				0.89 (0.07)				0.90 (0.07)				<0.001
Waist/height ratio	0.47 (0.04)				0.53 (0.04)				0.57 (0.04)				0.62 (0.04)				0.68 (0.06)				<0.001
Alcohol intake, g/day	3	0–13			3	0–11			1	0–8			2	0–7			1	0–4			<0.001
Smoking status[c]																					
Never			256	51			272	54			303	60			292	58			292	58	0.01
Former			112	22			116	23			122	24			120	24			132	26	0.14
Current			131	26			114	23			77	15			86	17			75	15	<0.001
Physical activity[c]																					
Inactive			139	28			169	34			167	33			174	35			210	42	<0.001
Moderately inactive			175	35			160	32			165	33			178	36			155	31	0.53
Moderately active			93	19			84	17			94	19			89	18			60	12	0.02
Active			89	18			84	17			71	14			59	12			71	14	0.02
Educational level[c]																					
None			10	2			10	2			28	6			21	4			38	8	<0.001
Primary school			166	33			227	45			248	49			248	50			254	51	<0.001
Technical/professional school			171	34			158	31			118	23			129	26			120	24	<0.001
Secondary school			92	18			67	13			72	14			60	12			51	10	<0.001
Longer (including university)			59	12			40	8			36	7			40	8			33	7	0.01
History of myocardial infarction[c]			13	3			17	3			14	3			25	5			24	5	0.02
History of stroke[c]			13	3			15	3			11	2			21	4			18	4	0.19
History of cancer[c]			18	4			28	6			26	6			20	4			23	5	0.88
Age at diabetes, years	51	42–57			52	45–58			53	46–57			53	48–58			52	47–57			<0.001
Diabetes duration, years	5	3–11			5	2–11			5	2–10			4	2–9			4	1–8			<0.001
Insulin use			201	40			123	24			88	17			85	17			99	20	<0.001

Abbreviations: IQR, interquartile range; SD, standard deviation.

[a] Continuous variables are shown as mean (SD) or median and IQR, and categorical variables are shown as number and percent.

[b] P_{trend} values across quintiles were calculated with a contrast statement in a general linear model.

[c] Denominator was decreased because of missing values.

Table 2. Hazard Rate Ratios for All-Cause Mortality Associated With Body Mass Index, Waist Circumference, Waist/Hip Ratio, and Waist/Height Ratio in 2,926 Men and 2,509 Women With Diabetes Mellitus at Baseline in 1992–2000 From the European Prospective Investigation Into Cancer and Nutrition

	Cases, no.	Person-Years	HRR[a]	95% CI	HRR[b]	95% CI	HRR[c]	95% CI
				Men				
Body mass index, kg/m^2								
≤24.9	96	5,322	1	Referent	1	Referent	1	Referent
25.0–27.1	91	5,287	1.02	0.76, 1.39	1.02	0.75, 1.39	0.67	0.45, 0.98
27.2–29.1	74	5,300	0.80	0.58, 1.11	0.81	0.58, 1.13	0.38	0.24, 0.60
29.2–31.8	93	5,314	1.07	0.79, 1.45	1.09	0.79, 1.52	0.39	0.24, 0.65
≥31.9	89	5,125	1.20	0.88, 1.63	1.23	0.89, 1.71	0.33	0.19, 0.60
P_{trend}[d]			0.21		0.15		<0.001	
Waist circumference, cm								
≤91.0	89	5,788	1	Referent	1	Referent	1	Referent
91.1–97.0	77	5,225	1.06	0.77, 1.45	1.07	0.76, 1.49	1.20	0.83, 1.72
97.1–103.0	73	5,021	1.03	0.75, 1.45	0.95	0.68, 1.34	1.24	0.82, 1.87
103.1–109.5	97	5,309	1.30	0.96, 1.76	1.31	0.94, 1.81	1.89	1.17, 3.05
≥109.6	107	5,006	1.51	1.11, 2.04	1.46	1.05, 2.01	2.11	1.23, 3.61
P_{trend}[d]			0.004		0.01		0.01	
Waist/hip ratio								
≤0.92	80	5,407	1	Referent	1	Referent	1	Referent
0.93–0.96	68	6,448	0.75	0.54, 1.05	0.80	0.57, 1.13	0.87	0.61, 1.24
0.97–0.99	87	5,318	1.16	0.84, 1.59	1.11	0.79, 1.55	1.21	0.85, 1.72
1.00–1.03	103	5,155	1.40	1.03, 1.92	1.45	1.05, 2.02	1.64	1.15, 2.35
≥1.04	105	4,022	1.72	1.26, 2.35	1.63	1.29, 2.41	1.99	1.36, 2.92
P_{trend}[d]			<0.001		<0.001		<0.001	
Waist/height ratio								
≤0.52	77	5,343	1	Referent	1	Referent	1	Referent
0.53–0.56	78	5,326	1.11	0.80, 1.54	1.09	0.77, 1.54	1.53	1.03, 2.27
0.57–0.59	92	5,286	1.43	1.04, 1.98	1.44	1.02, 2.01	2.74	1.73, 4.34
0.60–0.63	89	5,265	1.43	1.03, 1.98	1.47	1.04, 2.08	3.41	2.01, 5.78
≥0.64	107	5,130	1.93	1.40, 2.65	1.88	1.33, 2.65	4.85	2.66, 8.86
P_{trend}[d]			<0.001		<0.001		<0.001	

Table continues

Statistical analyses

All statistical analyses were performed with SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina). Hazard rate ratios and 95% confidence intervals of all-cause mortality were calculated by using Cox proportional hazard models separately for men and women (25). The proportional hazard assumption was tested with scaled Schoenfeld residuals and was not violated. Center and age at enrollment in 1-year categories were entered as stratum variables to control for differences in questionnaire design, follow-up procedures, and other nonmeasured center effects. Participants were followed from study entry until death, emigration, withdrawal, or end of the follow-up period. Age was used as the primary time variable with entry time defined as the subject's age in years at recruitment, and exit time was defined as the subject's age in years at death or censoring (lost to follow-up or end of the follow-up period). All reported *P* values are 2 sided.

Body mass index, waist circumference, waist/hip ratio, and waist/height ratio were analyzed in sex-specific quintiles. Median values within quintiles were tested as continuous variables in regression models to test for trend. Models for waist/height ratio were also calculated for body mass index strata. Restricted cubic spline regression models with 5 knots defined at the 5th, 25th, 50th, 75th, and 95th percentiles of body mass index, waist circumference, waist/hip ratio, and waist/height ratio were fit to provide further insight into the nature of the observed associations. Restricted cubic splines are a method of describing dose-response curves that make no prior assumptions about the shape of the curve (26). The significance of nonlinear spline terms was tested with a Wald chi-square test. Cause-specific risks of death were derived from competing risk models in which

Table 2. Continued

	Cases, no.	Person-Years	HRR[a]	95% CI	HRR[b]	95% CI	HRR[c]	95% CI
				Women				
Body mass index, kg/m^2								
≤24.7	37	4,678	1	Referent	1	Referent	1	Referent
24.8–27.6	39	4,675	0.89	0.55, 1.45	0.93	0.55, 1.56	0.75	0.40, 1.40
27.7–30.3	32	4,651	0.87	0.52, 1.44	1.04	0.60, 1.79	0.68	0.32, 1.44
30.4–33.5	48	4,523	1.21	0.76, 1.92	1.49	0.90, 2.46	0.75	0.34, 1.67
≥33.6	42	4,560	1.34	0.83, 2.14	1.61	0.95, 2.71	0.57	0.23, 1.39
P_{trend}[d]				0.08		0.02		0.26
Waist circumference, cm								
≤81.0	39	5,215	1	Referent	1	Referent	1	Referent
81.1–89.0	21	4,219	0.63	0.36, 1.11	0.67	0.36, 1.23	0.75	0.39, 1.45
89.1–95.8	42	4,657	1.06	0.66, 1.70	1.22	0.73, 2.04	1.49	0.76, 2.95
95.9–103.5	44	4,568	1.16	0.73, 1.86	1.46	0.88, 2.43	1.81	0.84, 3.94
≥103.6	52	4,428	1.69	1.08, 2.66	1.77	1.08, 2.92	2.19	0.94, 5.15
P_{trend}[d]				0.003		0.003		0.06
Waist/hip ratio								
≤0.81	35	5,704	1	Referent	1	Referent	1	Referent
0.82–0.85	38	4,694	1.48	0.90, 2.44	1.48	0.89, 2.48	1.47	0.86, 2.49
0.86–0.88	31	4,015	1.48	0.88, 2.48	1.57	0.91, 2.71	1.63	0.92, 2.90
0.89–0.92	40	4,412	1.52	0.93, 2.48	1.53	0.91, 2.58	1.48	0.85, 2.58
≥0.93	54	4,263	2.31	1.45, 3.68	2.30	1.40, 3.76	2.17	1.27, 3.71
P_{trend}[d]				0.002		0.002		0.01
Waist/height ratio								
≤0.50	35	4,750	1	Referent	1	Referent	1	Referent
0.51–0.55	31	4,662	1.00	0.59, 1.68	1.00	0.57, 1.74	1.19	0.62, 2.28
0.56–0.60	36	4,542	1.11	0.67, 1.84	1.33	0.78, 2.27	1.71	0.82, 3.58
0.61–0.65	42	4,628	1.18	0.73, 1.92	1.36	0.81, 2.30	1.78	0.79, 4.02
≥0.66	54	4,505	2.22	1.39, 3.55	2.46	1.46, 4.14	3.60	1.46, 8.85
P_{trend}[d]				<0.001		<0.001		0.003

Abbreviations: CI, confidence interval; HRR, hazard rate ratio.

[a] Model 1: Age and center stratified.

[b] Model 2: Model 1 adjusted for diabetes duration, insulin treatment, prevalent myocardial infarction, stroke, cancer, smoking status, smoking duration, smoking intensity, educational level, physical activity, and alcohol consumption.

[c] Model 3: Model 2 additionally adjusted for quintiles of waist/height ratio (when analyzing body mass index) or quintiles of body mass index (when analyzing waist circumference, waist/hip ratio, and waist/height ratio).

[d] P_{trend} values were calculated by using the median value within quintiles of the anthropometric measurement as a continuous variable.

separate regression coefficients for different causes were compared by using the Wald chi-square test and were derived from robust estimates of the covariance matrix (27, 28).

Statistical interaction for sex was tested with a likelihood ratio test by adding an interaction term and using the median value within quintiles as the continuous exposure variable. In addition, we checked whether the association of adiposity and mortality differed statistically between individuals with and without diabetes. Within the study population from EPIC used by Pischon et al. (8), we created sex- and diabetes-specific quintiles of anthropometry, used the median value within those quintiles, added a product term for diabetes status, and tested for statistical interaction with a likelihood ratio test.

Multivariate regression models were adjusted for diabetes duration (years), insulin treatment (yes/no), self-reported history of myocardial infarction, stroke, or cancer (yes/no/unknown or missing), smoking status (never/former (quit ≤10 years ago, 11–20 years ago, >20 years ago)/current (smoking duration ≤10 years, 11–20 years, 21–30 years, 31–40 years, >41 years, or unknown; <15, 15–24, or ≥25 cigarettes smoked daily/missing), educational level (none/primary school/technical or professional school/secondary school/longer (including university)/missing), physical activity (inactive/moderately inactive/moderately active/active/missing), and alcohol intake (0, >0–6, >6–18, >18–30, >30–60,

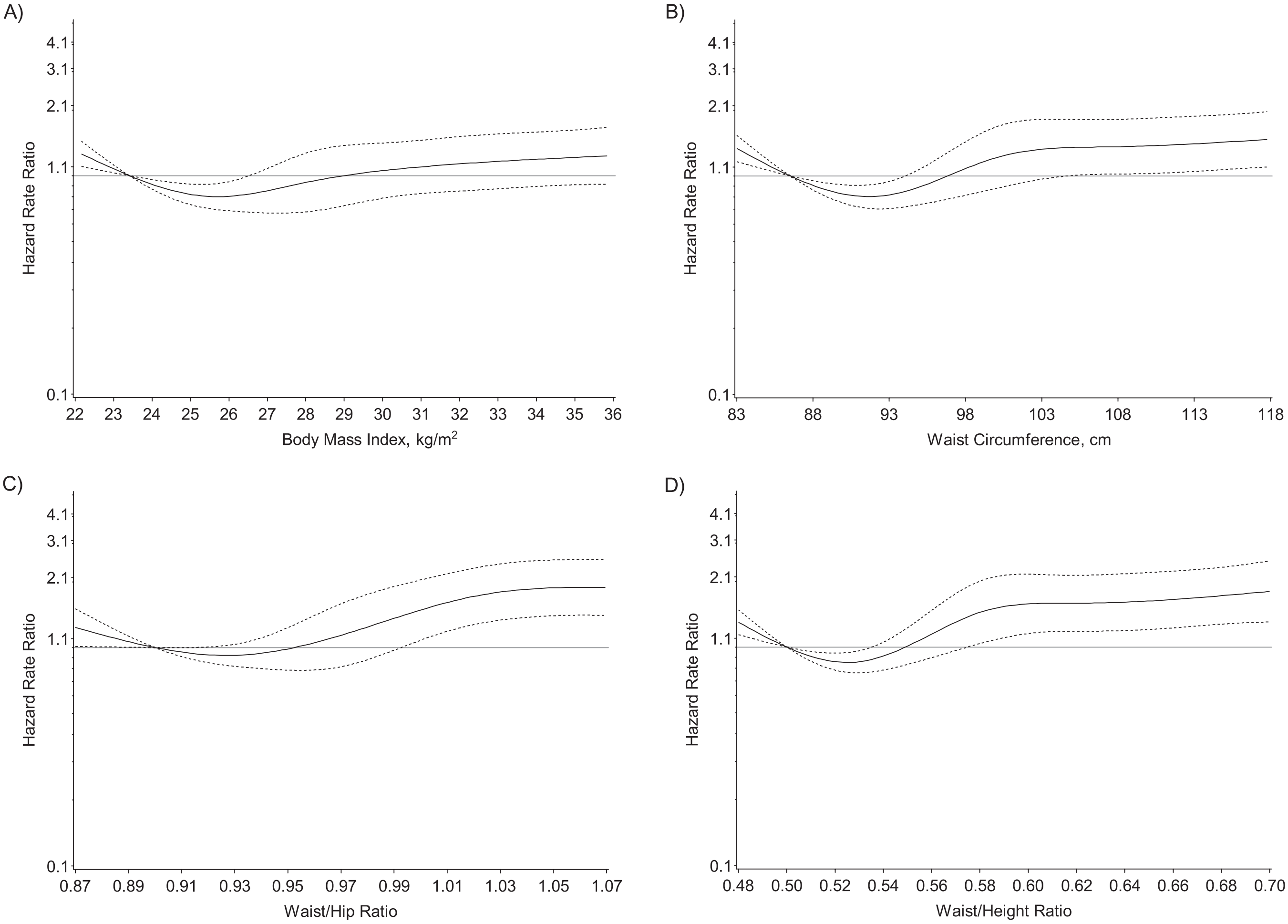

Figure 1. Adjusted hazard rate ratios of death among 2,926 European men with diabetes mellitus at baseline in 1992–2000 according to body mass index (A), waist circumference (B), waist/hip ratio (C), and waist/height ratio (D). Solid lines indicate hazard rate ratios, and dashed lines indicate 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 25th, 50th, 75th, and 95th percentiles of the sex-specific distribution, with the 10th percentile used as reference. Age- and study center-stratified models were adjusted for diabetes duration, insulin treatment, prevalent myocardial infarction, stroke, cancer, smoking status, smoking duration, smoking intensity, educational level, physical activity, and alcohol consumption. *P* values for nonlinearity were derived from a Wald chi-square test and were $P = 0.001$ for body mass index, $P < 0.0001$ for waist circumference, $P = 0.003$ for waist/hip ratio, and $P < 0.0001$ for waist/height ratio.

>60 g/day). A second model was additionally adjusted for quintiles of waist/height ratio when analyzing body mass index and for quintiles of body mass index when analyzing waist circumference, waist/hip ratio, and waist/height ratio.

To investigate the robustness of the results, we first attempted to exclude participants with type 1 diabetes by restricting the study population to participants who did not use insulin and were diagnosed above the age of 40 ($n = 1{,}525$ excluded). Furthermore, because comorbidities can confound the association between adiposity and mortality, we excluded participants who reported prevalent heart disease, stroke, and cancer at baseline ($n = 692$ excluded). Moreover, we investigated whether the difference in waist circumference measurement protocol influenced the estimates, and last, we excluded on study center at a time from the models to see whether the results were driven by a particular one.

RESULTS

At recruitment, participants of this prevalent diabetes cohort had a mean age of 57.3 (standard deviation, 6.3) years, a median diabetes duration of 4.6 (interquartile range, 2.0–9.8) years, and a mean body mass index of 28.9 (standard deviation, 4.9), and 22% reported insulin use. During follow-up (median = 9.3 years, interquartile range, 8.0–10.3), 641 participants died (172 from cardiovascular disease, 133 from cancer, and 150 from other known causes; 186 causes of deaths were unknown).

General characteristics according to sex-specific quintiles of body mass index are shown in Table 1. Participants with a high body mass index were older, less likely to use insulin, and had a shorter duration of diabetes. They also were diagnosed at an older age and were less educated and

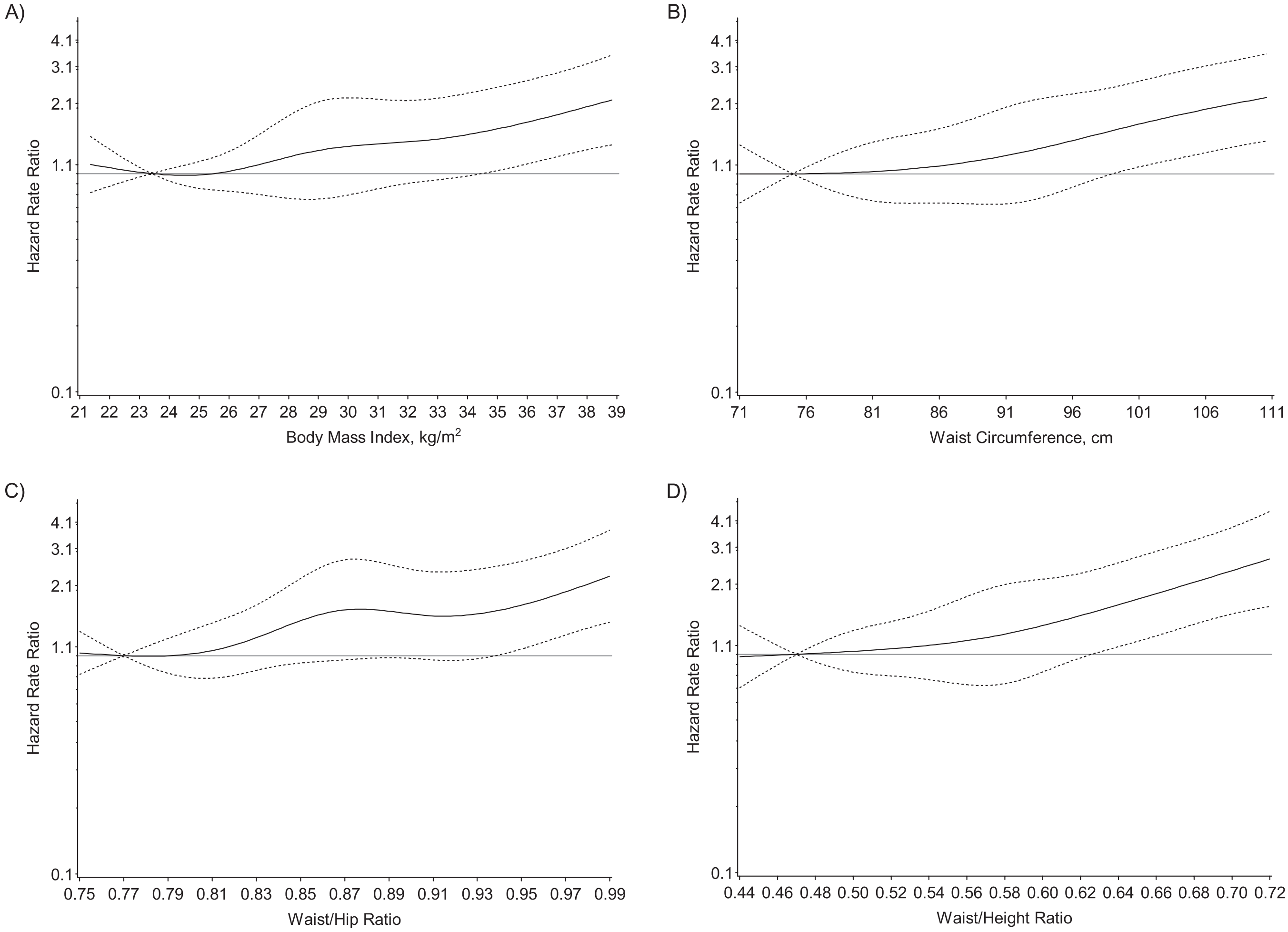

Figure 2. Adjusted hazard rate ratios of death among 2,509 European women with diabetes mellitus at baseline in 1992–2000 according to body mass index (A), waist circumference (B), waist/hip ratio (C), and waist/height ratio (D). Solid lines indicate hazard rate ratios, and dashed lines indicate 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 25th, 50th, 75th, and 95th percentiles of the sex-specific distribution, with the 10th percentile used as reference. Age- and study center-stratified models were adjusted for diabetes duration, insulin treatment, prevalent myocardial infarction, stroke, cancer, smoking status, smoking duration, smoking intensity, educational level, physical activity, and alcohol consumption. *P* values for nonlinearity were derived from a Wald chi-square test and were $P = 0.46$ for body mass index, $P = 0.86$ for waist circumference, $P = 0.56$ for waist/hip ratio, and $P = 0.61$ for waist/height ratio.

physically active than participants with a low body mass index. Men in the highest quintile had a higher alcohol consumption, whereas women with a high body mass index had a lower alcohol consumption and were also less likely to be a current smoker compared with leaner women. The same trends in baseline characteristics were observed across quintiles of waist/height ratio (data not shown).

Body mass index was slightly positive but not significantly associated with mortality in men: The hazard rate ratio in the 5th quintile was 1.23 (95% confidence interval (CI): 0.89, 1.71) (Table 2). All indicators of abdominal adiposity were positively associated with mortality in men. The strongest association was observed for waist/height ratio: The hazard rate ratio in the highest quintile was 1.88 (95% CI: 1.33, 2.65). After adjustment for waist/height ratio, an inverse relation between body mass index and mortality was observed (in the 5th quintile, the hazard rate ratio (HRR) = 0.33, 95% CI: 0.19, 0.60). Adjustment of body mass index in models of waist/height ratio led to a stronger association with a hazard rate ratio in the 5th quintile of 4.85 (95% CI: 2.66, 8.86) compared with the lowest. Wald chi-square tests for nonlinearity were significant ($P < 0.001$) for all anthropometric measurements in men (Figure 1). Figure 1 shows restricted cubic spline regression curves for the associations, which were not linear, but showed S-shaped curves.

Among women, there was a trend suggesting that body mass index was associated with mortality; however, the hazard rate ratios were not significant (Table 2). The pattern observed for measures of abdominal adiposity was similar to the one seen for men, although associations in general tended to be slightly weaker. The strongest association was

Table 3. Hazard Rate Ratios for All-Cause Mortality for Strata of Body Mass Index and Waist/Height Ratio in 5,435 European Men and Women with Diabetes Mellitus at Baseline in 1992–2000

Body Mass Index, kg/m^2	Waist/Height Ratio, ≤0.57			Waist/Height Ratio, ≥0.58		
	Cases, no.	HRR[a]	95% CI	Cases, no.	HRR[a]	95% CI
			Men			
≤28.1	183	1	Referent	43	1.51	1.05, 2.17
≥28.2	21	0.77	0.48, 1.25	196	1.24	0.98, 1.56
			Women			
≤28.8	79	1	Referent	19	1.49	0.83, 2.67
≥28.9	7	0.90	0.38, 2.11	93	1.43	1.01, 2.02

Abbreviations: CI, confidence interval; HRR, hazard rate ratio.

[a] Age and center stratified and adjusted for sex, diabetes duration, insulin treatment, prevalent myocardial infarction, stroke, cancer, smoking status, smoking duration, smoking intensity, educational level, physical activity, and alcohol consumption.

observed for waist/height ratio: The hazard rate ratio between the extreme quintiles was 2.46 (95% CI: 1.46, 4.14). Adjustment for body mass index led to a hazard rate ratio of 3.60 (95% CI: 1.46, 8.85) for comparison of extreme quintiles. In contrast to men, mutual adjustment did not strengthen but attenuated the associations of body mass index, waist circumference, and mortality. The restricted cubic spline regression curves did not give evidence for nonlinear relations among women (Figure 2).

Table 3 confirms that the associations of waist/height ratio and mortality were independent from body mass index: Men and women with a low waist/height ratio did not have increased mortality risk, irrespective of their body mass index stratum.

In cause-specific mortality analyses, strong associations for waist/height ratio and cardiovascular mortality and mortality due to noncardiovascular disease/noncancer causes were observed among men (Table 4). Furthermore, waist circumference was related to increased cancer mortality and waist/hip ratio to a higher risk of death due to other known causes. *P* values for differences between causes of death derived from the competing risk model did not show significant differences.

No statistical interaction was found between measures of adiposity and sex. When probable type 1 diabetes patients and participants with comorbidities were excluded, the observed associations for the measures of abdominal adiposity largely remained. When women who were probable type 1 cases were excluded, an inverse relation was seen between body mass index and mortality when adjusted for waist/height ratio (in the 5th quintile, HRR = 0.28, 95% CI: 0.09, 0.92). Furthermore, when those women with comorbidities at baseline were excluded, a high body mass index was associated with an increased risk of death without adjustment (in the 5th quintile, HRR = 2.25, 95% CI: 1.23, 4.12). The difference in waist circumference measurement protocol between study centers did not lead to a different conclusion (data not shown). Excluding one study center at a time hardly affected the findings (data not shown).

No statistical interaction was found between adiposity and diabetes status in relation to mortality. Respectively for men and women, $P_{\text{interaction}}$ values were 0.22 and 0.09 for body mass index, 0.36 and 0.10 for waist circumference, 0.13 and 0.24 for waist/hip ratio, and 0.32 and 0.07 for waist/height ratio.

DISCUSSION

In men and women with diabetes mellitus, indicators of abdominal obesity, that is, waist circumference, waist/hip ratio, and waist/height ratio, were positively associated with mortality. These associations seemed to be independent from general obesity and were nonlinear for men. Compared with other measurements, waist/height ratio showed the strongest association with mortality. Body mass index, as an indicator of general obesity, was not independently positive associated with mortality in men or women with diabetes. Detailed analyses did not show stronger associations for cardiovascular disease mortality compared with death due to other causes.

The strongest associations were observed for waist/height ratio. Waist/height ratio has not been investigated as an indicator for abdominal obesity as often as waist circumference and waist/hip ratio, but it has been shown to carry more information than the other anthropometric indices in predicting cardiovascular risk factors and mortality in the general population (29–32). Waist/height ratio comprises 2 measurements: Waist circumference reflects the amount of abdominal fat, and height is also associated with adverse outcomes (22, 32). Furthermore, it has been shown that individuals with a shorter stature have a higher percentage of body fat compared with people of the same body mass index (33). Moreover, height is inversely related to overall mortality (34). Therefore, waist/height ratio is suggested to be a relevant measurement of relative fat distribution among participants of different ages and statures (22). In 2 cross-sectional studies in persons with diabetes, waist/height ratio suggested the strongest association with coronary artery disease (35) and adverse cardiorenal outcomes (36) compared with body mass index, waist circumference, and waist/hip ratio. To our knowledge, this is the first prospective study investigating the relation

Table 4. Hazard Rate Ratios[a] for Cause-specific Mortality Associated With Body Mass Index, Waist Circumference, Waist/Hip Ratio, and Waist/Height Ratio in 5,249 European Men and Women With Diabetes Mellitus at Baseline in 1992–2000

	Cardiovascular Disease			Cancer			Other Known Causes		
	Cases, no.	HRR[b]	95% CI	Cases, no.	HRR[b]	95% CI	Cases, no.	HRR[b]	95% CI
Men									
Body mass index, kg/m^2									
≤26.4	42	1	Referent	24	1	Referent	41	1	Referent
26.5–29.9	35	0.76	0.45, 1.28	32	1.30	0.71, 2.40	28	0.94	0.54, 1.61
≥30.0	47	1.09	0.66, 1.80	27	1.35	0.70, 2.58	37	1.68	0.96, 2.94
Waist circumference, cm									
≤95.1	39	1	Referent	16	1	Referent	35	1	Referent
95.2–104.5	31	0.78	0.45, 1.35	39	3.38	1.67, 6.83	31	1.18	0.68, 2.05
≥104.6	54	1.16	0.71, 1.89	28	2.79	1.31, 5.95	40	1.70	0.98, 2.94
Waist/hip ratio									
≤0.95	37	1	Referent	25	1	Referent	32	1	Referent
0.96–1.00	36	0.87	0.51, 1.50	28	1.52	0.81, 2.85	28	1.13	0.64, 2.01
≥1.01	51	1.56	0.94, 2.57	30	1.77	0.95, 3.31	46	2.03	1.19, 3.44
Waist/height ratio									
≤0.55	33	1	Referent	22	1	Referent	36	1	Referent
0.56–0.61	32	0.93	0.53, 1.62	34	1.63	0.87, 3.05	27	1.02	0.58, 1.78
≥0.62	59	1.72	1.02, 2.90	27	1.70	0.86, 3.36	43	2.13	1.23, 3.70
Women									
Body mass index, kg/m^2									
≤26.6	14	1	Referent	14	1	Referent	16	1	Referent
26.7–31.2	16	1.31	0.51, 3.39	19	1.18	0.52, 2.69	10	0.86	0.30, 2.48
≥31.3	18	1.68	0.65, 4.33	17	1.46	0.63, 3.40	18	2.63	0.98, 7.05
Waist circumference, cm									
≤86.5	12	1	Referent	12	1	Referent	15	1	Referent
86.6–98.0	19	2.05	0.75, 5.60	14	0.82	0.35, 1.96	10	0.65	0.21, 1.98
≥98.1	17	2.70	0.94, 7.75	24	2.07	0.92, 4.62	19	1.86	0.74, 4.66
Waist/hip ratio									
≤0.83	8	1	Referent	17	1	Referent	13	1	Referent
0.84–0.89	16	2.41	0.75, 7.78	11	0.42	0.17, 1.03	19	1.96	0.71, 5.41
≥0.90	24	4.63	1.47, 14.57	22	1.04	0.48, 2.22	12	1.29	0.44, 3.78
Waist/height ratio									
≤0.54	12	1	Referent	16	1	Referent	14	1	Referent
0.55–0.61	16	1.99	0.71, 5.54	15	0.82	0.36, 1.86	12	1.19	0.41, 3.48
≥0.62	20	2.48	0.89, 6.91	19	1.00	0.44, 2.28	18	1.90	0.73, 4.93

Abbreviations: CI, confidence interval; HRR, hazard rate ratio.
[a] Participants with unknown cause of death were not included.
[b] Age and center stratified and adjusted for diabetes duration, insulin treatment, prevalent myocardial infarction, stroke, cancer, smoking status, duration, and intensity, educational level, physical activity, and alcohol consumption.

between waist/height ratio and mortality in individuals with diabetes.

Pischon et al. (8) investigated the association between general and abdominal obesity and risk of death in the overall EPIC study population ($n = 359,387$). Participants in the lower and upper body mass index categories had an increased risk of death, and abdominal obesity as measured by waist circumference and waist/hip ratio was strongly associated with mortality after adjustment for body mass index. In contrast to the general population, results of the present study suggest that abdominal obesity plays a more important role than general adiposity for mortality in persons with diabetes. This can be due to the fact that obesity is strongly related to development of diabetes mellitus type 2 (37), and heterogeneity of body mass index might be lower than heterogeneity in measures of abdominal obesity in this population. However, investigating the question if associations differed for individuals with or without diabetes, no statistical interaction for diabetes status was found. Therefore, associations were not different for diabetic individuals compared with nondiabetic individuals when analyzed irrespective of the absolute value of the anthropometric measurement, because the quintiles were diabetes specific. This indicates that the differences in associations that we have observed between diabetics and nondiabetics are probably caused by differences in absolute levels of adiposity.

Prospective studies into the relation between body mass index and mortality in individuals with diabetes mellitus have shown heterogeneous results. Some investigations observed an inverse association between body mass index and mortality (9–12). Two other cohort studies demonstrated that a high body mass index was related to increased mortality (14, 18) and coronary heart disease (13). Body mass index was not associated with risk of death in 2 other studies when the level of exercise capacity was taken into account (15, 19), and 2 investigations found a U- or J-shaped relation between body mass index and mortality (16, 17). In the EURODIAB Prospective Complications Study, waist/hip ratio was negatively associated with overall, cardiovascular disease, and noncardiovascular disease mortality, whereas no association was observed for body mass index (21). However, this study population was restricted to persons with type 1 diabetes. Moreover, Sone et al. (20) observed that waist circumference was not associated with cardiovascular disease incidence in Japanese diabetes patients. Of note, associations in these studies were not adjusted for other anthropometric measurements. Finally, these inconsistent results and our findings suggest that body mass index alone is not an adequately sufficient measure when investigating the association between adiposity and mortality in individuals with diabetes.

The observed associations between measures of abdominal adiposity and mortality tended to be stronger in men than in women after adjustment for body mass index. This can be due to gender differences in body fat distribution. In men, fat tissue tends to accumulate in the abdominal area, whereas in women gluteofemoral obesity is more common (38). This is underlined by the fact that the associations between waist/hip ratio and mortality were most similar for both sexes compared with the other measurements. Furthermore, a higher body mass index—independent of waist/height ratio—was associated with decreased mortality in men. When waist circumference is held constant, body mass index may indicate lean body mass, whereas waist measurements, independent of body mass index, are indices of abdominal fat mass (39). Adjusting the relation of waist circumference and mortality for body mass index means the modeling of waist circumference when body mass index and, thus, body weight are kept constant. An increase in the waist circumference, without an increase in weight, would, therefore, indicate an increase in peripheral fat mass and a decrease in muscle mass.

The subjects with low body mass index might have been more severe cases of diabetes, because the proportion of insulin users was higher and the median diabetes duration was longer. We examined the influence of prevalent cardiovascular disease and cancer in sensitivity analyses. These showed that women who were ill at baseline or were more severe diabetes cases confounded the association between body mass index and mortality. Severe illness will lead to a decrease in fat mass as well as muscle mass and will, therefore, be more reflected in body mass index. Moreover, women with a higher body mass index probably benefited from their energy stores (40). This can explain why some studies observed that a high body mass index was related to a decreased mortality risk (9–12). Thus, reverse causality from other prevalent and/or subclinical diseases might have influenced our estimates (41).

The percentage of cardiovascular disease deaths was relatively low (3), and cause-specific analyses were hampered by small numbers in our study. Diabetes has been predominantly associated with increased cardiovascular disease mortality (3, 4), but we also found increased risks for cancer in men and death due to other (noncancer/noncardiovascular disease) known causes (5, 42). In our study, most cancers were due to cancer of the lung, pancreas, and breast. These may have developed as a consequence of the diabetes status (42), but obesity too is associated with cancer risk (43).

Our study had some limitations that should be considered when interpreting the results. First, self-reports of diabetes at baseline were confirmed with a second information source, but when no additional information source was available, we were unable to discriminate true- from false-positive case classifications, which might have introduced selection bias into our study. Furthermore, although a few false negative cases were found, no systematic screening for them was conducted. Therefore, this cohort of prevalent diabetic individuals can best be considered as a convenience subsample. Second, there is debate whether or not to include mutual adjustments of anthropometric measurements. Because the measurements were highly correlated in this study population, adjustment may induce collinearity. However, modeling the residual variables of the measurements as a method to overcome this high correlation did not change the results.

In conclusion, measurements of abdominal but not general adiposity were associated with increased risk of death in diabetic men and women. The waist/height ratio showed the strongest association. Further investigation is needed to analyze its value in mortality risk prediction models in individuals with diabetes.

ACKNOWLEDGMENTS

Author affiliations: Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany (Diewertje Sluik, Heiner Boeing, Jukka Montonen, Tobias Pischon, Ute Nöthlings); German Cancer Research Center, Heidelberg, Germany (Rudolf Kaaks, Birgit Teucher); Danish Cancer Society, Institute of Cancer Epidemiology, Copenhagen, Denmark (Anne Tjønneland, Jytte Halkjaer); Institute for Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark (Tina L. Berentzen); Department of Epidemiology, School of Public Health, Aarhus University, Aarhus, Denmark (Kim Overvad); Department of Cardiology, Center for

Cardiovascular Research, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark (Kim Overvad); Public Health Department of Gipuzkoa, Basque Government, San Sebastian, Spain (Larraitz Arriola); CIBER de Epidemiología y Salud Pública, Barcelona, Spain (Larraitz Arriola, Eva Ardanaz); Public Health Institute of Navarra, Pamplona, Spain (Eva Ardanaz); Molecular and Nutritional Epidemiology Unit, Istituto per lo Studio e la Prevenzione Oncologica, Florence, Italy (Benedetta Bendinelli); Nutritional Epidemiology Unit, IRCCS Istituto Nazionale Tumori, Milan, Italy (Sara Grioni); Cancer Registry and Histopathology Unit, "Civile M. P. Arezzo" Hospital, Ragusa, Italy (Rosario Tumino); Center for Cancer Prevention (Piedmont), Turin, Italy (Carlotta Sacerdote); Human Genetic Foundation, Turin, Italy (Carlotta Sacerdote); Department of Clinical and Experimental Medicine, Federico II University, Naples, Italy (Amalia Mattiello); Center for Prevention and Health Services Research, National Institute for Public Health and the Environment, Bilthoven, the Netherlands (Annemieke M. W. Spijkerman); Center for Nutrition and Health, National Institute for Public Health and the Environment, Bilthoven, the Netherlands (Daphne L. van der A); Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands (Joline W. Beulens, Yvonne T. van der Schouw); Department of Clinical Sciences, Lund University Hospital, Malmö, Sweden (Peter M. Nilsson, Bo Hedblad); Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden (Olov Rolandsson, Paul W. Franks); and Epidemiology Section, Institute for Experimental Medicine, Christian-Albrechts-University of Kiel, Kiel, Germany (Ute Nöthlings).

This study was supported by a European Foundation for the Study of Diabetes (EFSD)/Sanofi-Aventis grant.

The sponsor did not have any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Conflict of interest: none declared.

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes—2007. *Diabetes Care*. 2007;30(suppl 1):S4–S41.
2. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care*. 2007;30(1):162–172.
3. Berry C, Tardif JC, Bourassa MG. Coronary heart disease in patients with diabetes. Part I: Recent advances in prevention and noninvasive management. *J Am Coll Cardiol*. 2007;49(6):631–642.
4. Woodward M, Zhang X, Barzi F, et al. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. *Diabetes Care*. 2003;26(2):360–366.
5. Vigneri P, Frasca F, Sciacca L, et al. Diabetes and cancer. *Endocr Relat Cancer*. 2009;16(4):1103–1123.
6. Bantle JP, Wylie-Rosett J, Albright AL, et al. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. American Diabetes Association. *Diabetes Care*. 2008;31(suppl 1):S61–S78.
7. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Prospective Studies Collaboration. *Lancet*. 2009;373(9669):1083–1096.
8. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med*. 2008;359(20):2105–2120.
9. Weiss A, Boaz M, Beloosesky Y, et al. Body mass index and risk of all-cause and cardiovascular mortality in hospitalized elderly patients with diabetes mellitus. *Diabet Med*. 2009;26(3):253–259.
10. Zoppini G, Verlato G, Leuzinger C, et al. Body mass index and the risk of mortality in type II diabetic patients from Verona. *Int J Obes Relat Metab Disord*. 2003;27(2):281–285.
11. McEwen LN, Kim C, Karter AJ, et al. Risk factors for mortality among patients with diabetes: the Translating Research Into Action for Diabetes (TRIAD) Study. *Diabetes Care*. 2007;30(7):1736–1741.
12. Chaturvedi N, Stevens LK, Fuller JH. Mortality and morbidity associated with body weight in people with IDDM. The WHO Multinational Study of Vascular Disease in Diabetes. *Diabetes Care*. 1995;18(6):761–765.
13. Cho E, Manson JE, Stampfer MJ, et al. A prospective study of obesity and risk of coronary heart disease among diabetic women. *Diabetes Care*. 2002;25(7):1142–1148.
14. Eeg-Olofsson K, Cederholm J, Nilsson PM, et al. Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 13,087 patients. *Diabetologia*. 2009;52(1):65–73.
15. Church TS, Cheng YJ, Earnest CP, et al. Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care*. 2004;27(1):83–88.
16. Khalangot M, Tronko M, Kravchenko V, et al. Body mass index and the risk of total and cardiovascular mortality among patients with type 2 diabetes: a large prospective study in Ukraine. *Heart*. 2009;95(6):454–460.
17. Ross C, Langer RD, Barrett-Connor E. Given diabetes, is fat better than thin? *Diabetes Care*. 1997;20(4):650–652.
18. Chaturvedi N, Fuller JH. Mortality risk by body weight and weight change in people with NIDDM. The WHO Multinational Study of Vascular Disease in Diabetes. *Diabetes Care*. 1995;18(6):766–774.
19. McAuley PA, Myers JN, Abella JP, et al. Exercise capacity and body mass as predictors of mortality among male veterans with type 2 diabetes. *Diabetes Care*. 2007;30(6):1539–1543.
20. Sone H, Tanaka S, Iimuro S, et al. Waist circumference as a cardiovascular and metabolic risk in Japanese patients with type 2 diabetes. *Obesity (Silver Spring)*. 2009;17(3):585–592.
21. Soedamah-Muthu SS, Chaturvedi N, Witte DR, et al. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). *Diabetes Care*. 2008;31(7):1360–1366.
22. Ashwell M, Hsieh SD. Six reasons why the waist-to-height ratio is a rapid and effective global indicator for health risks of obesity and how its use could simplify the international public health message on obesity. *Int J Food Sci Nutr*. 2005;56(5):303–307.

23. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr*. 2002;5(6B):1113–1124.
24. Ross R, Berentzen T, Bradshaw AJ, et al. Does the relationship between waist circumference, morbidity and mortality depend on measurement protocol for waist circumference? *Obes Rev*. 2008;9(4):312–325.
25. Cox DR, Oakes D. *Analysis of Survival Data*. London, United Kingdom: Chapman and Hall; 1984.
26. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989;8(5):551–561.
27. Lunn M, McNeil D. Applying Cox regression to competing risks. *Biometrics*. 1995;51(2):524–532.
28. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *Am J Epidemiol*. 2005;162(10):975–982.
29. Cox BD, Whichelow MJ, Prevost AT. The development of cardiovascular disease in relation to anthropometric indices and hypertension in British adults. *Int J Obes Relat Metab Disord*. 1998;22(10):966–973.
30. Ho SY, Lam TH, Janus ED. Waist to stature ratio is more strongly associated with cardiovascular risk factors than other simple anthropometric indices. *Ann Epidemiol*. 2003;13(10):683–691.
31. Huxley R, Mendis S, Zheleznyakov E, et al. Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk—a review of the literature. *Eur J Clin Nutr*. 2010;64(1):16–22.
32. Hsieh SD, Muto T. The superiority of waist-to-height ratio as an anthropometric index to evaluate clustering of coronary risk factors among non-obese men and women. *Prev Med*. 2005;40(2):216–220.
33. López-Alvarenga JC, Montesinos-Cabrera RA, Velázquez-Alva C, et al. Short stature is related to high body fat composition despite body mass index in a Mexican population. *Arch Med Res*. 2003;34(2):137–140.
34. Engeland A, Bjørge T, Selmer RM, et al. Height and body mass index in relation to total mortality. *Epidemiology*. 2003;14(3):293–299.
35. Tseng CH. Waist-to-height ratio and coronary artery disease in Taiwanese type 2 diabetic patients. *Obesity (Silver Spring)*. 2008;16(12):2754–2759.
36. Lamacchia O, Pinnelli S, Camarchio D, et al. Waist-to-height ratio is the best anthropometric index in association with adverse cardiorenal outcomes in type 2 diabetes mellitus patients. *Am J Nephrol*. 2009;29(6):615–619.
37. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet*. 2005;365(9467):1333–1346.
38. Stevens J, Katz EG, Huxley RR. Associations between gender, age and waist circumference. *Eur J Clin Nutr*. 2010;64(1):6–15.
39. Moore SC. Waist versus weight: which matters more for mortality? *Am J Clin Nutr*. 2009;89(4):1003–1004.
40. Wells JC. The evolution of human fatness and susceptibility to obesity: an ethological approach. *Biol Rev Camb Philos Soc*. 2006;81(2):183–205.
41. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes (Lond)*. 2008;32(6):959–966.
42. Ogunleye AA, Ogston SA, Morris AD, et al. A cohort study of the risk of cancer associated with type 2 diabetes. *Br J Cancer*. 2009;101(7):1199–1201.
43. Pischon T, Nöthlings U, Boeing H. Obesity and cancer. *Proc Nutr Soc*. 2008;67(2):128–145.