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Relation between body mass index, waist circumference, and cardiovascular outcomes in 19,579 diabetic patients with established vascular disease: the REACH Registry

Jean Dallongeville[1], Deepak L Bhatt[2], Ph Gabriel Steg[3–5], Philippe Ravaud[6], Peter W Wilson[7], Kim A Eagle[8], Shinya Goto[9], Jean-Louis Mas[10], Gilles Montalescot[11] (for the REACH Registry Investigators)

Abstract

Aims: Obesity is frequent in type 2 diabetic patients with myocardial infarction (MI) or established cardiovascular disease. Earlier studies suggest that elevated body mass index (BMI) is associated with a favorable prognosis for persons with established vascular disease. We sought to analyse the associations between raised BMI and waist circumference with the 2-year event rate in type 2 diabetic patients with established vascular disease.

Methods and results: Patients from the Reduction of Atherothrombosis for Continued Health (REACH) Registry, an international, prospective cohort of patients at high risk of atherothrombosis, were selected if they were diabetic and had established atherosclerotic arterial disease ($n = 19{,}579$). The main outcomes after 2-year follow-up were: all-cause death, cardiovascular death, MI, stroke, cardiovascular death/MI/stroke, and cardiovascular death/MI/stroke/rehospitalization. The rates of all-cause death, cardiovascular death, and cardiovascular death/MI/stroke decreased across increasing BMI quintile categories, whereas the same rates were stable across waist categories. The hazard ratios, adjusted for confounders, decreased significantly with increasing BMI for all-cause death ($p < 0.0001$), cardiovascular death ($p = 0.0009$), cardiovascular death/MI/stroke ($p = 0.0004$), and all events ($p = 0.002$), but not for greater waist circumference.

Conclusion: There is an apparent obesity paradox (better outcome with increasing obesity) when obesity is measured by BMI but not when measured by waist circumference in diabetic subjects.

Keywords

Body mass index, cardiovascular outcomes, diabetes, vascular disease, waist circumference, obesity, metabolic syndrome

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Introduction

Obesity is a risk factor for increased mortality and cardiovascular disease in the general population.[1,2] In contrast, in patients with established vascular disease

[1]Institut Pasteur de Lille, France; INSERM, U744, Lille, France.
[2]VA Boston Healthcare System, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA.
[3]INSERM U698, Paris, France.
[4]Université Paris 7, Paris, France.
[5]Hôpital Bichat Claude Bernard, AP-HP, Paris, France.
[6]Centre d'Epidémiologie Clinique, INSERM U738, Paris, France.
[7]Cardiology Division, Emory University School of Medicine, Atlanta, GA, USA.
[8]University of Michigan Cardiovascular Center, Ann Arbor, MI, USA.
[9]Tokai University School of Medicine, Isehara, Japan.
[10]Paris-Descartes University, INSERM U894, Department of Neurology, Hôpital Sainte-Anne, Paris, France.
[11]Service de Cardiologie, Pitié-Salpétrière Hospital, AP-HP, INSERM U856, Université Paris 6, Paris, France.

Corresponding author:
Jean Dallongeville, Institut Pasteur de Lille, INSERM U744, 1 rue du Pr Calmette, 59019 Lille Cedex, France
Email: jean.dallongeville@pasteur-lille.fr

and those undergoing percutaneous coronary intervention or after an acute coronary syndrome, raised body mass index (BMI) appears to be associated with a favorable prognosis: the so-called 'obesity paradox'.[3,4] A similar relationship is also reported in patients with heart failure, hypertension, and end-stage renal disease.[5–7]

Type 2 diabetes is associated with increased coronary artery disease (CAD) risk in the general population.[8,9] The intensity of this risk, however, has been a matter of debate. One study reported that type 2 diabetic patients have the same risk of CAD death as non-diabetic subjects with a history of myocardial infarction (MI),[10,11] but this observation has not been confirmed in other studies.[12–15] Patients with diabetes have more extensive atherosclerosis, accelerated plaque progression, and a markedly increased risk of adverse events after MI or angioplasty.[16,17] The mechanism of this association is related to altered cardiovascular risk factors, as well as endothelial dysfunction, platelet aggregation, and inflammatory processes.

Obesity is frequent in type 2 diabetic patients with MI (reaching 54.8% in the USA) or established cardiovascular disease.[18] To the best of our knowledge, the prognostic impact of total and abdominal obesity on recurrent events in diabetic patients with established atherothrombosis is unknown. The goal of the present study was to analyse the associations between raised BMI and waist circumference with the 2-year event rate in diabetic patients with established vascular disease.

Methods

Full details of the rationale and design of the Reduction of Atherothrombosis for Continued Health (REACH) Registry have been described elsewhere.[19,20] The REACH Registry is a prospective, observational study of more than 68,000 outpatients from approximately 5000 sites in 44 countries. The study design was approved by the institutional review board in each participating country, and participants provided written informed consent to participate. Family and general practitioners made up 44% of the recruiting physicians; others were specialists in internal medicine (29%), cardiology (13%), neurology (9%), endocrinology (2%), general surgery (2%), and vascular disease (1%).[19,20]

Subjects

Physician participating to the study diagnosed and reported diabetes from their patients' records. In the present analysis, we considered all diabetic patients with established vascular disease. Our final sample consisted of 19,579 subjects. Patients enrolled were aged $\geq$45 years with at least one of the following: (1) CAD (angina, MI, coronary angioplasty, stent implantation, or bypass surgery); (2) cerebrovascular disease (CVD) (ischaemic stroke or transient ischaemic attack (TIA)); or (3) peripheral arterial disease [PAD; historical or current intermittent claudication associated with ankle-brachial index (ABI) <0.9]. Patients already in a clinical trial, hospitalized patients, and those who might have difficulty returning for a follow-up visit were excluded. Patients were evaluated at baseline for a range of demographic, medical, and laboratory characteristics, before being re-evaluated annually for up to 48 months post baseline to ascertain whether they experienced any clinical events or hospitalizations.

Definition of cardiovascular risk factors

Data were collected using a standardized international case report form, which was completed at the study visit. Baseline height, weight, waist circumference, systolic and diastolic blood pressure, and available fasting glucose and cholesterol levels were obtained. From these data, baseline demographic and risk factor characteristics were analysed. Current smoking was defined as $\geq$5 cigarettes/day on average within the month before entry into the REACH Registry.

Follow-up

Follow-up data (at 24 months) were collected from participating physicians from medical records, and included clinical outcomes, treatment, and physical or biological data.[21] Although events were not adjudicated, reports of ischaemic stroke and TIA had to be sourced from a neurologist or hospital to ensure a reliable diagnosis. Endpoint definitions were: (a) all-cause death; (b) cardiovascular death, including fatal stroke, fatal MI, and other cardiovascular death (including other death of cardiac origin; pulmonary embolism; any sudden death; death following a vascular operation, vascular procedure, or amputation (except for trauma or malignancy); death attributed to heart failure; death following a visceral or limb infarction, and any other death that could not be attributed definitely to a non-vascular cause or haemorrhage); (c) non-fatal MI; (d) non-fatal stroke; (e) cardiovascular death/MI/stroke; and (f) cardiovascular death/MI/stroke/rehospitalization for an atherothrombotic event.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation. Categorical variables are expressed as frequencies and percentages. Patients were separated into quintiles of BMI and waist

circumference distribution. Age- and sex-related event rates were computed for each quintile of distribution. Multivariable hazard ratios (HRs) were calculated with Cox regression using the second quintile as the reference group. Covariables were selected *a priori* and included: age, sex, smoking, hypertension, hypercholesterolaemia, symptomatic disease, number of affected vascular beds, physician's medical specialty, lipid-lowering therapy, antihypertensive agents, antiplatelets, beta-blockers, oral antidiabetic drugs, and insulin. Trend analyses were performed using BMI or waist categories as continuous variables. Statistical analyses were conducted using SAS version 9.1 software (SAS Institute Inc, Cary, NC).

Results

Baseline characteristics according to BMI

The baseline demographics, clinical characteristics, and treatments of the 19,579 diabetic patients with established vascular disease are presented in Table 1 by quintile of BMI. The higher BMI quintiles had a lower mean age ($p < 0.0001$), but more women ($p < 0.0001$), Caucasians ($p < 0.0001$), former smokers ($p < 0.0001$), and patients with a history of raised blood pressure ($p < 0.0001$). Mean systolic and diastolic blood pressure levels ($p < 0.0001$), and concentrations of triglycerides ($p < 0.0001$) and glycaemia ($p = 0.0005$) (but not cholesterol) were higher in the upper than the lower quintile of BMI distribution. With respect to vascular disease, there were more patients with CAD ($p < 0.0001$) than with stroke or PAD, and these patients less frequently had multiple vascular bed disease ($p < 0.0028$) in the highest than lowest quintile of BMI distribution. In general, patients in the higher BMI quintiles received more medications than those in the lower BMI groups. Fewer obese patients achieved target blood pressure, triglycerides, and glycaemia goals, but cholesterol levels were similar across quintiles.

Baseline characteristics according to waist circumference

Baseline demographics, clinical characteristics and treatments by quintile of waist circumference are also presented in Table 1. The mean age was lower ($p < 0.0001$) and there were more Caucasians ($p < 0.0001$) and former smokers ($p < 0.0001$) in the higher quintiles of waist distribution. In contrast, there were fewer women ($p < 0.0001$) in the highest quintile than in the lowest. Increased waist circumference was associated with a history of hypertension ($p < 0.0001$). Mean blood pressure ($p = 0.0024$), triglycerides ($p < 0.0001$) and glycaemia ($p < 0.0001$), but not cholesterol levels, were higher in the upper than in the lower quintile of waist circumference distribution. With respect to vascular disease, there were more patients with CAD ($p < 0.0001$) and fewer with stroke ($p < 0.0001$) in the highest quintiles of waist distribution. In contrast to BMI, these patients more frequently had multiple vascular bed disease ($p < 0.0001$) in the highest than in the lowest quintile of waist distribution. Patients in the higher waist quintiles received more medications than those in the lower waist groups. Subjects with abdominal obesity were less likely to achieve target blood pressure, triglycerides, and glycaemia goals but more likely to reach cholesterol goals.

Relationship between BMI/waist circumference and event rates

Figure 1 shows the age- and sex-adjusted event rates across quintiles of BMI and waist circumference. The rates of all-cause death (p trend < 0.005), non-fatal stroke ($p < 0.008$), and cardiovascular death/MI/stroke ($p < 0.002$) decreased across increasing BMI categories. The rates of all events (including rehospitalization) rose from the first quintile to the third and then decreased. In contrast, the rates of all-cause death (p trend < 0.05) and all events ($p < 0.0007$) rose between the lowest and highest quintile of waist distribution. There were no other statistically significant trends.

Adjusted HRs of the relationship between BMI/waist circumference and event rates

Compared with the second quintile of BMI distribution (which was used as a reference; HR defined as 1), patients in the lowest quintile of BMI distribution had a higher risk of all-cause death, cardiovascular death, and cardiovascular death/MI/stroke (Table 2). Increasing BMI was associated with decreasing trends in all-cause death, cardiovascular death, non-fatal MI, cardiovascular death/MI/stroke and all events (including rehospitalization). In contrast, there were no associations between increasing waist circumference and adjusted HRs of any of these events.

Subgroup analyses for cardiovascular death/MI/stroke are presented in Figure 2. There was no evidence for heterogeneity between sex, age, ethnicity, smoking, hypertension, hypercholesterolaemia, raised triglycerides, and affected vascular bed groups. Results for additional end-points are presented in the supplementary material online appendix.

Discussion

In the present study, we have analysed the relationships between BMI and waist circumference with 2-year rates of death, cardiovascular events, and rehospitalization in 19,579 diabetic patients with established vascular disease.

Table 1. Characteristics at baseline and treatment of diabetic patients with symptomatic disease ($n = 19{,}579$) according to body mass index and waist circumference quintiles

	Body mass index quintiles (kg/m^2)						Waist circumference quintiles (cm)					
	Q1 (24.32)	Q2 (24.33–26.93)	Q3 (26.94–29.43)	Q4 (29.44–33.06)	Q5 (33.07)	*p* (trend)	Q1 (88.0)	Q2 (88.1–96.0)	Q3 (96.1–103.0)	Q4 (103.1–111.8)	Q5 (111.9)	*p* (trend)
n	3912	3931	3914	3912	3910		3886	3519	3821	3637	3623	
Age (years)	70.4 ± 9.5	69.7 ± 9.3	68.7 ± 9.3	67.6 ± 9.4	65.6 ± 9.1	<0.0001	69.5 ± 9.6	68.7 ± 9.6	68.9 ± 9.4	68.1 ± 9.3	66.8 ± 9.2	<0.0001
Female	35.6	30.8	29.3	33.2	43.2	<0.0001	47.1	33.5	31.7	28.2	30.3	<0.0001
Ethnic origin						<0.0001						<0.0001
Caucasian	38.1	56.3	66.0	73.3	79.4		35.7	53.6	67.0	76.6	80.9	
Hispanic	5.1	5.9	6.5	6.2	4.8		5.3	6.4	6.9	5.8	4.5	
East Asian	37.0	20.8	10.6	5.2	1.6		39.4	22.2	9.0	3.8	1.3	
South Asian	2.8	2.1	1.7	1.2	0.4		2.9	2.1	1.8	1.0	0.7	
Other Asian	12.1	8.2	5.8	3.9	2.2		11.4	8.4	6.1	3.7	2.0	
Black	2.7	3.0	5.0	6.4	8.7		3.1	4.1	5.4	5.5	6.5	
Other	2.3	3.6	4.4	4.0	2.9		2.2	3.2	3.9	3.6	4.3	
Smoking						<0.0001						<0.0001
Current	13.7	13.0	12.6	11.5	12.0		12.7	13.0	12.1	12.5	12.3	
Former	39.0	43.9	45.6	48.4	45.6		34.4	42.4	46.4	49.3	51.1	
Never	47.3	43.1	41.8	40.1	42.5		52.9	44.6	41.5	38.2	36.6	
History of HBP	80.1	84.6	87.5	90.2	92.8	<0.0001	81.3	85.2	87.7	89.4	91.3	<0.0001
DBP (mmHg)	75.7 ± 11.3	77.0 ± 11.2	78.4 ± 11.3	78.6 ± 11.7	77.9 ± 11.5	<0.0001	76.5 ± 11.6	77.5 ± 11.2	77.6 ± 11.4	77.9 ± 11.4	78.3 ± 11.7	<0.0001
SBP (mmHg)	136.2 ± 20.1	137.6 ± 19.0	138.9 ± 19.9	138.8 ± 19.7	137.9 ± 19.1	<0.0001	137.2 ± 20.0	137.7 ± 19.7	138.0 ± 19.5	137.7 ± 19.2	138.9 ± 19.4	0.0024
Total cholesterol >200 mg/dl	34.4	34.1	35.5	34.6	32.9	0.26	37.5	34.1	33.3	32.9	33.3	0.0005
Total cholesterol (mg/dl)	188.3 ± 45.8	187.3 ± 48.2	190.5 ± 51.0	189.2 ± 50.4	187.4 ± 48.3	0.039	191.4 ± 47.0	188.1 ± 47.7	188.2 ± 50.1	187.3 ± 50.4	187.9 ± 49.1	0.009
Total triglycerides >150 mg/dl	37.1	44.8	51.0	55.1	59.9	<0.0001	39.6	43.8	50.0	55.8	58.9	<0.0001
Total triglycerides (mg/dl)	149.6 ± 94.0	163.1 ± 98.3	177.3 ± 105.5	187.3 ± 110.8	197.1 ± 117.1	<0.0001	153.5 ± 95.0	163.1 ± 99.3	175.6 ± 105.5	186.3 ± 110.0	196.5 ± 116.7	<0.0001
Raised glycaemia (≥126 mg/dl)	67.4	71.3	75.0	75.7	78.0	<0.0001	69.1	71.1	72.3	75.9	78.5	<0.0001
Glycaemia (mg/dl)	144.8 ± 56.3	143.7 ± 50.7	144.7 ± 50.7	145.9 ± 53.1	149.1 ± 56.7	0.0005	144.7 ± 55.2	142.7 ± 50.6	144.4 ± 53.0	145.8 ± 51.9	150.2 ± 55.4	<0.0001
Number of affected vessel locations						0.0028						<0.0001
1	77.5	77.3	75.6	76.7	78.9		79.8	78.5	75.9	76.1	75.0	
2	19.2	20.3	21.4	21.0	18.7		18.1	18.8	21.2	21.3	22.0	
3	3.3	2.4	3.0	2.3	2.4		2.1	2.7	2.9	2.6	3.0	
Disease locations												
CAD	64.6	71.7	75.5	77.6	81.2	<0.0001	66.0	70.5	75.4	78.3	80.5	<0.0001

Stroke	41.5	34.9	34.0	31.0	27.8	<0.0001	40.1	36.7	33.5	30.0	29.3	<0.0001
PAD	19.6	18.6	17.9	17.1	14.5	<0.0001	16.1	17.0	18.2	18.2	18.1	0.064
Medication												<0.0001
Antiplatelets	82.8	84.3	84.1	83.7	82.0	0.034	83.3	84.5	84.1	83.1	82.0	0.047
Lipid-lowering agents	64.9	74.6	79.4	81.8	83.3	<0.0001	67.3	74.6	78.9	81.8	81.9	<0.0001
Beta-blockers	39.7	49.4	54.2	57.3	59.8	<0.0001	61.9	68.8	73.4	76.1	75.7	<0.0001
ACE inhibitors	41.1	49.3	53.6	55.2	56.3	<0.0001	10.1	12.1	13.8	14.3	15.7	<0.0001
Angiotensin II blockers	24.3	24.6	24.1	26.4	28.0	0.001	39.9	48.9	52.7	57.2	57.4	<0.0001
Other antihypertensives	8.8	10.1	11.1	12.6	14.5	<0.0001	9.2	9.2	11.6	12.6	14.1	<0.0001
Antidiabetics	85.5	87.0	87.7	88.4	91.4	<0.0001	85.8	86.5	88.3	88.6	90.3	<0.0001
Insulin	23.1	25.3	26.3	30.2	37.3	<0.0001	23.5	23.1	27.4	30.4	35.8	<0.0001
Biguanides	31.1	34.8	39.5	40.8	43.3	<0.0001	31.7	35.6	38.8	41.6	42.4	<0.0001
Sulphonylureas	45.5	44.7	43.3	42.0	41.3	0.0006	44.8	45.1	44.7	41.3	41.1	<0.0001
Thiazol	9.5	11.2	13.8	16.5	24.2	<0.0001	10.8	11.4	15.5	16.9	19.7	<0.0001
Other	14.4	11.6	9.9	9.1	8.7	<0.0001	14.6	11.1	9.8	9.3	9.0	<0.0001

Values are means ± SD or %. CAD, coronary artery disease; DBP, diastolic blood pressure; HBP, high blood pressure; PAD, peripheral arterial disease; Q, quintile; SBP, systolic blood pressure.

Greater BMI was associated with better prognosis for all-cause death, cardiovascular death, and composite end-points including rehospitalization. In contrast, waist circumference, a marker of visceral adiposity, showed no association with outcomes. These results extend the observation of an 'obesity paradox' to diabetic patients and show that waist circumference measurement does not predict vascular outcomes reliably in diabetic patients with established vascular disease.

BMI was inversely associated with age- and sex-adjusted crude rates of death and cardiovascular events (Figure 1). Adjustment for confounders attenuated this association, suggesting that covariables such as age, sex, smoking, risk factors, and treatment contribute to the paradoxical prognosis in obese diabetic subjects. Indeed, the characteristics of the subjects in the highest quintiles of BMI distribution differed greatly from those of the subjects in the lowest quintiles. Similar differences between obese and lean

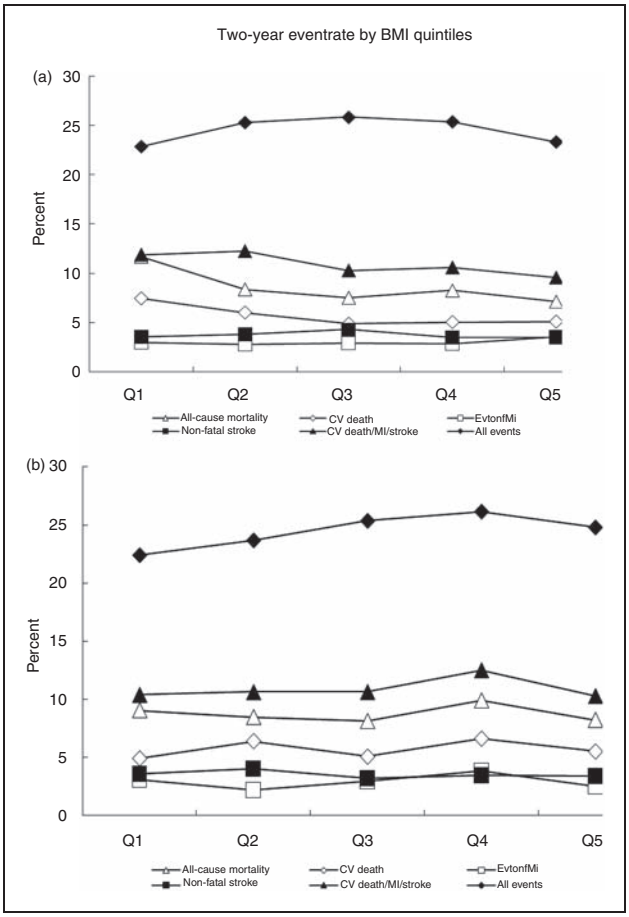

Figure 1. Two-year event rates adjusted for age and sex according to body mass index (A) and waist circumference (B) quintiles in symptomatic and diabetic patients
CV, cardiovascular; MI, myocardial infarction.

Table 2. Hazard ratios and 95% CI of events according to body mass index and waist circumference quintiles adjusted for age, sex, geographic area, smoking, hypertension, hypercholesterolaemia, symptomatic, number of vascular beds, specialty, lipid-lowering agents, antihypertensive agents, antiplatelets, beta-blockers, oral antidiabetic agents, and insulin for symptomatic and diabetic patients

	Body mass index quintiles (kg/m^2)						Waist circumference quintiles (cm)[a]					
	Q1 (24.32)	Q2 (24.33–26.93)	Q3 (26.94–29.43)	Q4 (29.44–33.06)	Q5 (33.07)	*p* (trend)	Q1 (88.0)	Q2 (88.1–96.0)	Q3 (96.1–103.0)	Q4 (103.1–111.8)	Q5 (111.9)	*p* (trend)
n	3912	3931	3914	3912	3910		3886	3519	3821	3637	3623	
All-cause death	1.38 (1.16–1.63)	1	0.96 (0.80–1.15)	0.92 (0.76–1.11)	0.86 (0.71–1.05)	<0.0001	1.18 (0.97–1.43)	1	1.13 (0.93–1.36)	1.07 (0.88–1.30)	1.07 (0.88–1.31)	0.54
CV death	1.35 (1.09–1.67)	1	0.96 (0.77–1.20)	0.84 (0.66–1.06)	0.97 (0.77–1.23)	0.0009	1.10 (0.86–1.39)	1	1.04 (0.83–1.31)	0.96 (0.76–1.22)	1.00 (0.79–1.27)	0.87
Non-fatal MI	1.22 (0.91–1.63)	1	0.93 (0.69–1.25)	0.98 (0.73–1.30)	0.70 (0.51–1.95)	0.017	1.37 (1.00–1.88)	1	1.07 (0.78–1.47)	1.17 (0.86–1.60)	0.86 (0.62–1.21)	0.060
Non-fatal stroke	0.97 (0.75–1.24)	1	0.93 (0.72–1.21)	1.02 (0.79–1.33)	0.79 (0.59–1.06)	0.45	0.91 (0.71–1.18)	1	0.85 (0.65–1.12)	0.99 (0.76–1.30)	0.94 (0.71–1.25)	0.77
CV death/MI/stroke	1.17 (1.01–1.35)	1	0.92 (0.79–1.07)	0.89 (0.76–1.04)	0.82 (0.70–0.97)	0.0004	1.08 (0.92–1.27)	1	1.00 (0.86–1.17)	1.10 (0.86–1.18)	0.93 (0.79–1.10)	0.53
CV death/MI/stroke/ hospitalization (all events)	1.01 (0.92–1.11)	1	0.96 (0.87–1.05)	0.92 (0.83–1.01)	0.83 (0.75–0.92)	0.002	1.06 (0.96–1.17)	1	0.99 (0.90–1.09)	0.97 (0.88–1.08)	0.90 (0.81–1.00)	0.061

Values are hazard ratios (95% CI). CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; Q, quintile. [a]Missing data for waist circumference for 1093 patients.

patients have been reported in other databases reporting a paradoxical association between BMI and outcomes in patients with established CAD.[22–24] Overall, our findings in diabetic patients do not differ markedly from those of earlier studies in patients with hypertension[25] or in non-selected CAD patients.[3,4] In the latter studies, diabetes was an important confounder associated with both obesity and prognosis. Our results suggest that diabetes is not likely to affect the relationship in CAD patients.

Waist circumference is strongly correlated with intra-abdominal adipose tissue and metabolic disorders and, in the general population, is associated with CAD events occurrence.[26] In the present study, waist circumference showed neither an inverse relationship with cardiovascular event rates nor a positive relationship, despite being associated with metabolic disorders such as hypertriglyceridaemia, dyslipidaemia, and hypertension. Earlier studies that assessed the prognosis of CAD patients in relation to waist girth or waist-to-hip ratio have found mixed results: no associations were found between waist girth and outcomes in some[27,28] but not all[29,30] studies.

Several hypotheses have been proposed to explain the inverse association between BMI and cardiovascular events. From a pathophysiological point of view, there is no doubt that adipose tissue accumulation triggers an inflammatory response that is responsible for altered lipid and glucose metabolism and vascular damage. In the general population, BMI and waist circumference are convenient surrogate measures of body fat, but this may not be the case (particularly for BMI) in patients with established CAD. Indeed, sarcopenia, muscle wasting, and inanition are associated with reduced BMI and poor prognosis and may be more common in older patients with established atherosclerosis.[3] It has also been proposed that patients with higher BMI have a greater metabolic reserve that protects them from complications in the context of heart failure. Finally, given their worse cardiometabolic risk profile, obese subjects may be more likely to receive care, as suggested by the larger proportion of obese subjects receiving cardiovascular treatment. Although statistical adjustments were performed, the likelihood of residual confounding effects in this observational study is not negligible. Furthermore, the differences in baseline characteristics could hamper the possibility of comparing the prognosis. Even if statistical adjustments were used to control confounders, the likely residual effect is important.

The present study has various strengths and limitations. The REACH Registry is a large cohort of 19,579 diabetic patients with atherothrombosis receiving contemporary therapies. However, given its observational design, no causal inference can be drawn from

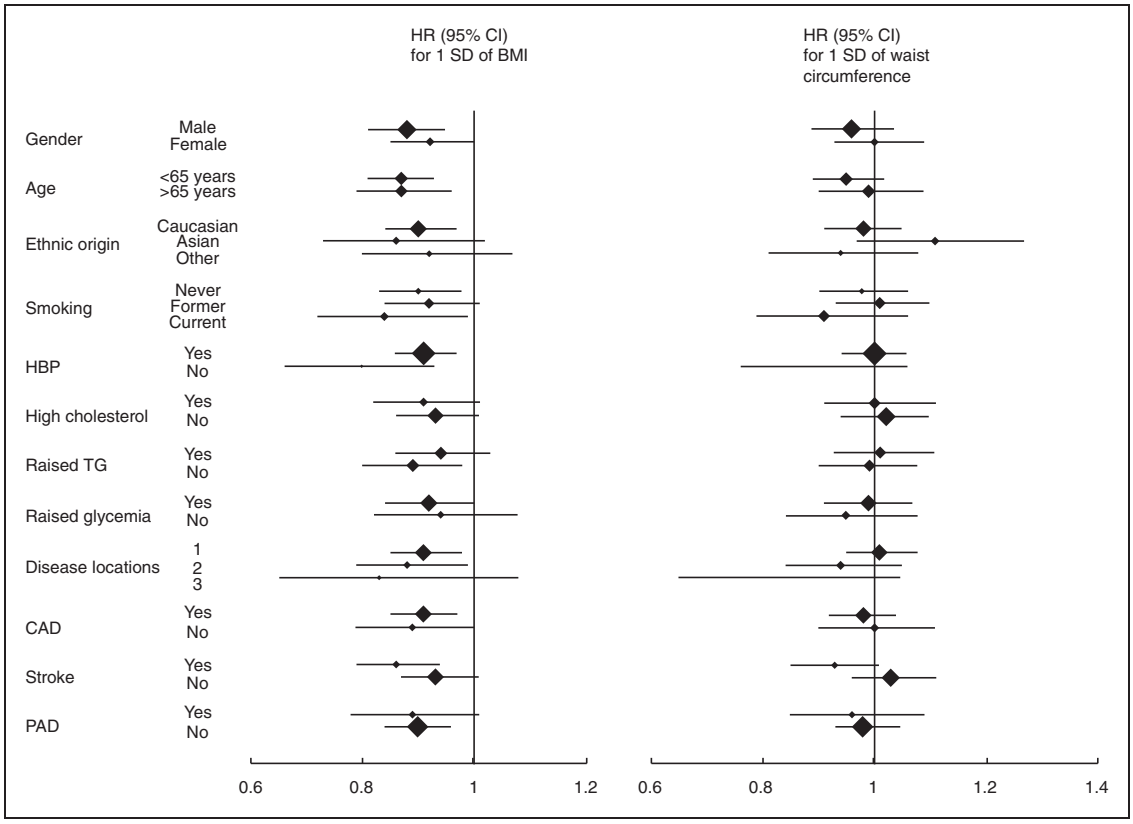

Figure 2. Hazard ratios and 95% confidence intervals for cardiovascular death/myocardial infarction/stroke per one standard deviation increase in body mass index or waist circumference CAD, coronary artery disease; HBP, high blood pressure; PAD, peripheral arterial disease; TG, triglycerides.

the conclusions. The 2-year follow-up rate was high, with data collected from >95% of patients, with no noticeable dropout. However, 2 years is a relatively short time period, and with much longer follow-up a relationship may have emerged between waist circumference and adverse ischaemic outcomes. Most patients were receiving recommended treatments in line with current guidelines for diabetes care, but less than half reached treatment goals for glycaemia. However, as with most observational studies, the baseline characteristics of the subjects were not matched. Changes in body weight after the index event were not recorded, making it impossible to assess potential effects of weight change (intentional or unintentional) on prognosis.

The clinical implications of these findings are that BMI and waist measurements cannot be used as simple markers to assess the risk of future complications in diabetic patients with established vascular diseases. Additionally, pharmacotherapies that are designed to decrease weight should not be assumed to reduce clinical cardiovascular events. Furthermore, owing to the possibility of residual confounders, one should not conclude that weight reduction is unnecessary or harmful in diabetic patients with established coronary heart disease. Intentional weight loss is associated with an improvement in cardiovascular risk profile and better long-term prognosis in obese subjects and diabetic patients with coronary heart disease.

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References

1. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; 373(9669): 1083–1096.
2. McGee DL. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol* 2005; 15(2): 87–97.
3. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006; 368(9536): 666–678.
4. Oreopoulos A, Padwal R, Norris CM, Mullen JC, Pretorius V and Kalantar-Zadeh K. Effect of obesity on short- and long-term mortality postcoronary revascularization: a meta-analysis. *Obesity (Silver Spring)* 2008; 16(2): 442–450.
5. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM and McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008; 156(1): 13–22.
6. Lavie CJ, Osman AF, Milani RV and Mehra MR. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. *Am J Cardiol* 2003; 91(7): 891–894.
7. Lavie CJ, Mehra MR and Milani RV. Obesity and heart failure prognosis: paradox or reverse epidemiology? *Eur Heart J* 2005; 26(1): 5–7.
8. Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch Intern Med* 2001; 161(14): 1717–1723.
9. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106(25): 3143–31421.
10. Haffner SM, Lehto S, Ronnemaa T, Pyorala K and Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; 339(4): 229–234.
11. Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, et al. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. *Diabetes Care* 1998; 21(1): 69–75.
12. Natarajan S, Liao Y, Cao G, Lipsitz SR and McGee DL. Sex differences in risk for coronary heart disease mortality associated with diabetes and established coronary heart disease. *Arch Intern Med* 2003; 163(14): 1735–1740.
13. Vaccaro O, Eberly LE, Neaton JD, Yang L, Riccardi G and Stamler J. Impact of diabetes and previous myocardial infarction on long-term survival: 25-year mortality follow-up of primary screenees of the Multiple Risk Factor Intervention Trial. *Arch Intern Med* 2004; 164(13): 1438–1443.

14. Lee CD, Folsom AR, Pankow JS and Brancati FL. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. *Circulation* 2004; 109(7): 855–860.
15. Krempf M, Parhofer KG, Steg PG, Bhatt DL, Ohman EM, Rother J, et al. Cardiovascular event rates in diabetic and nondiabetic individuals with and without established atherothrombosis (from the REduction of Atherothrombosis for Continued Health [REACH] Registry). *Am J Cardiol* 2010; 105(5): 667–671.
16. Nicholls SJ, Tuzcu EM, Kalidindi S, Wolski K, Moon KW, Sipahi I, et al. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials. *J Am Coll Cardiol* 2008; 52(4): 255–262.
17. Flaherty JD and Davidson CJ. Diabetes and coronary revascularization. *JAMA* 2005; 293(12): 1501–1508.
18. De Bacquer D, Dallongeville J, Heidrich J, Kotseva K, Reiner Z, Gaita D, et al. Management of overweight and obese patients with coronary heart disease across Europe. *Eur J Cardiovasc Prev Rehabil* 2010; 17(4): 447–454.
19. Ohman EM, Bhatt DL, Steg PG, Goto S, Hirsch AT, Liau CS, et al. The REduction of Atherothrombosis for Continued Health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. *Am Heart J* 2006; 151(4): 786–10.
20. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; 295(2): 180–189.
21. Steg PG, Bhatt DL, Wilson PW, D'Agostino Sr R, Ohman EM, Rother J, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007; 297(11): 1197–1206.
22. Kennedy LM, Dickstein K, Anker SD, Kristianson K and Willenheimer R. The prognostic importance of body mass index after complicated myocardial infarction. *J Am Coll Cardiol* 2005; 45(1): 156–158.
23. Mak KH, Bhatt DL, Shao M, Haffner SM, Hamm CW, Hankey GJ, et al. The influence of body mass index on mortality and bleeding among patients with or at high-risk of atherothrombotic disease. *Eur Heart J* 2009; 30(7): 857–865.
24. Abdulla J, Kober L, Abildstrom SZ, Christensen E, James WP and Torp-Pedersen C. Impact of obesity as a mortality predictor in high-risk patients with myocardial infarction or chronic heart failure: a pooled analysis of five registries. *Eur Heart J* 2008; 29(5): 594–601.
25. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q, et al. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med* 2007; 120(10): 863–870.
26. Gruson E, Montaye M, Kee F, Wagner A, Bingham A, Ruidavets JB, et al. Anthropometric assessment of abdominal obesity and coronary heart disease risk in men: the PRIME study. *Heart* 2010; 96(2): 136–140.
27. Zeller M, Steg PG, Ravisy J, Lorgis L, Laurent Y, Sicard P, et al. Relation between body mass index, waist circumference, and death after acute myocardial infarction. *Circulation* 2008; 118(5): 482–490.
28. Canoy D, Boekholdt SM, Wareham N, Luben R, Welch A, Bingham S, et al. Body fat distribution and risk of coronary heart disease in men and women in the European Prospective Investigation Into Cancer and Nutrition in Norfolk cohort: a population-based prospective study. *Circulation* 2007; 116(25): 2933–2943.
29. Kragelund C, Hassager C, Hildebrandt P, Torp-Pedersen C and Kober L. Impact of obesity on long-term prognosis following acute myocardial infarction. *Int J Cardiol* 2005; 98(1): 123–131.
30. Dagenais GR, Yi Q, Mann JF, Bosch J, Pogue J and Yusuf S. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. *Am Heart J* 2005; 149(1): 54–60.