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Cardiovascular risk in relation to body mass index and use of evidence-based preventive medications in patients with or at risk of atherothrombosis

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Aim Explore the relation between body mass index (BMI) and cardiovascular disease, and the influence of optimal medical therapy (OMT) on this relationship.

Methods and results Patients from the REACH cohort, an international, prospective cohort of patients with or at high risk of atherosclerosis with documentation of potential confounders, including treatments and risk factors, were followed up to 4 years ($n = 54\,285$). Patients were categorized according to baseline BMI (ranging from underweight to Grade III obesity). Optimal medical therapy was defined as the use of the four cardioprotective medication classes (statins, ACE inhibitors/angiotensin II receptor blockers, β-blockers, and antiplatelet agents). The main outcomes were all-cause mortality, cardiovascular (CV) mortality, and CV events. In primary and secondary prevention, a reverse J-shaped curve best described the relationship between BMI categories and the incidence of the various outcomes. In secondary prevention, the highest adjusted risks were observed for underweight patients (1.97, $P < 0.01$, and 1.29, $P = 0.03$, for CV mortality and CV events) and the lowest HRs were observed, respectively, in Grade II and Grade III obese patients (0.73, $P < 0.01$ and 0.80, $P < 0.01$). The proportion of patients on OMT increased with BMI from 10.1 to 36% ($P < 0.001$). The apparent CV protection conferred by obesity persisted in patients receiving OMT.

Conclusion An obesity paradox was observed in both primary and secondary CV prevention patients. The intensity of use of evidence-based preventive medications does not account for the paradoxical CV protection associated with obesity. At extremes of BMI, further interventions beyond OMT may be needed to reduce CV risk.

Keywords Obesity • Paradox • Cardiovascular disease • Epidemiology • Optimal therapy

Introduction

Epidemiological and clinical studies in the general population have demonstrated that overweight and obesity increase the risk of developing chronic conditions such as diabetes, dyslipidaemia, hypertension, and cancers, and are associated with all-cause and cardiovascular (CV) morbidity and mortality, independently of gender, age, and ethnicity.[1–3] However, a growing body of literature, including large meta-analyses, has recently revealed a phenomenon called the 'obesity paradox'.[4,5] Indeed, obesity has been associated with better survival in some groups of patients, such as individuals with heart failure,[6] diabetes,[7] or chronic kidney disease,[8] and in patients with a history of coronary heart disease (CHD).[9–11] Azimi *et al.*[12] suggested that moderate overweight was beneficial, but that severe obesity was detrimental for patients with documented coronary atherosclerosis. Despite the well-known limitations of

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observational studies, Dixon *et al.*,[13] in a commentary on the obesity paradox, considered that a body mass index (BMI) in the obese range may provide a survival advantage compared with that in the normal range. It may therefore be preferable to focus on good quality nutrition and physical activity rather than intentional weight loss, which has uncertain effects.[13] On the other hand, for others, the obesity paradox does not reflect a causal effect, but may be due to bias or confounding.[14] In particular, Schenkeveld *et al.*[11] proposed the influence of more optimal therapy in obese patients. More optimal therapy of obese patients, when not taken into account in the analysis, acts as a confounding factor and consequently distorts the association between weight and outcomes. Although a higher BMI has been associated with the use of more medications,[11,12,15] large-scale data focusing on the use of cardioprotective drugs according to BMI, especially in people with a history of atherothrombotic events, are lacking.

This study was designed to evaluate the relationship between BMI and CV morbidity and mortality in the Reduction of Atherothrombosis for Continued Health (REACH) cohort, a population with high CV risk and extensive documentation of treatment and risk factors. We investigated the intensity of medication use according to BMI category, distinguishing high-risk patients in primary CV prevention from patients with a history of prior CV event. We then determined whether optimal medical therapy (OMT) in this secondary prevention group affects the relationship between BMI and CV events.

Methods

Full details of the rationale and design of the REACH registry have been described previously.[16] The study design was approved by local ethics boards and participants provided their written consent to participate.

Subjects

The REACH Registry is a prospective, observational study conducted in >5000 centres in 44 countries. Recruitment was done by general practitioners as well as specialists. A total of 69 055 consecutive outpatients at least 45 years old with ≥3 risk factors for atherosclerosis and patients with documented cardiovascular disease (CVD) (coronary, cerebrovascular, or peripheral artery disease) were enrolled between 2003 and 2004. The multiple risk factors category consisted of diabetes, diabetic nephropathy, symptomatic or asymptomatic ankle-brachial index ≤0.9, asymptomatic carotid artery stenosis ≥70%, carotid intima-media thickness at least twice that at adjacent sites, systolic blood pressure ≥150 mmHg despite treatment, hypercholesterolaemia treated with medication, current smoking ≥15 cigarettes per day, and age ≥65 years for men or ≥70 years for women. The study design, selection of physicians,[16] and baseline and follow-up experience of patients in the REACH Registry[17–19] have been previously published. The initial follow-up was planned for 2 years, and shortly before that time point, an additional 2-year extension was proposed. Not all countries and sites participating in the 2-year follow-up cohort decided to continue participation in the registry, largely for financial reasons, although the majority did. Only countries and sites that participated in the 4-year follow-up were included in the present analysis.

Data collection

Data were collected at baseline and were then re-evaluated annually for up to 4 years by the physicians participating in the study. Follow-up was completed in 2008. The patients' demographic, clinical, and laboratory characteristics were evaluated at baseline. Body mass index was calculated as weight in kilograms divided by height in meters squared. Baseline systolic and diastolic blood pressure, waist circumference, and most recently available fasting glucose and cholesterol levels were obtained. Treatments taken regularly by the patients, including antiplatelet agents, oral anticoagulants, lipid-lowering agents, CV medications, and antidiabetic agents at the time of enrolment were recorded. Cardiovascular risk factors consisted of those documented in the patient's medical records or for which patients were receiving treatment: diabetes (any history of diabetes or current diabetes diagnosed by at least two fasting blood glucose assays >126 mg/dL, treated or not), hypertension previously or currently treated, and smoking status (never, former, and current).

Definition of optimal medical therapy

Optimal medical therapy was defined as the use of all four types of medication known to reduce the incidence of CV events in patients at very high risk of CVD, particularly in the context of secondary prevention: statins, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), β-blockers, and antiplatelet agents, including aspirin.[20] Suboptimal therapy was defined as the prescription of one or none of the four recommended medications, to allow comparisons of extreme situations (optimal vs. suboptimal therapy).

Outcomes

Outcomes in the REACH registry have been previously described.[16] Three outcomes were considered in the present study: (i) all-cause mortality, (ii) CV mortality, and (iii) CV events including CV death, stroke, or myocardial infarction. Outcomes were recorded by participating physicians from medical records. Endpoints were not adjudicated, although stroke required documentation by a neurologist or hospital medical record.

Statistical analysis

Categorical variables are expressed as frequencies and percentage, and continuous variables are expressed as mean ± standard deviation. Patients in primary and secondary prevention were analysed separately. Each of these two subpopulations was segmented, in line with the World Health Organization classification system,[21] into five subgroups according to BMI: <18 kg/m^2 (underweight), 18–24.9 kg/m^2 (normal weight), 25–29.9 kg/m^2 (overweight), 30–34.9 kg/m^2 (Grade I obesity), 35–39.9 kg/m^2 (Grade II obesity), and ≥40 kg/m^2 (Grade III obesity). For sensitivity analyses, patients were separated into quintiles of waist circumference distribution (available for 46 968 patients). Multivariate hazard ratios (HRs) for the outcomes studied for each group of BMI or waist circumference were estimated by Cox regression models using the normal BMI group and the lowest quintile of waist circumference as reference, respectively. Covariates were selected a priori on the basis of their association with BMI (*Table 1*). These included age, gender, baseline cholesterol (divided into tertiles), systolic blood pressure (divided into tertiles), diastolic blood pressure (divided into tertiles), fasting triglycerides (divided into tertiles) and baseline serum creatinine (divided into tertiles), baseline diabetic status, at least one antiplatelet agent, at least one antidiabetic agent, at least one lipid-lowering agent, diuretic use, current smoking (yes/no), and region (North America, Western Europe, and other). We have tested associations between BMI group and each covariate in the Cox model using Cramer's V statistics. All results were lower or equal to 0.25, which indicates a weak association between adjustment covariates and BMI group.

Trend analyses were performed using BMI categories as continuous variables. The *P*-value was calculated after adjusting for diabetes, gender, geographic region, systolic and diastolic blood pressure, total

Table 1 Baseline characteristics of the primary prevention cohort by BMI category

BMI classes	Primary prevention (n = 9779)						P
	1 (n = 66)	2 (n = 2286)	3 (n = 3452)	4 (n = 2344)	5 (n = 993)	6 (n = 638)	
Age	72.69 (9.9)	71.79 (9.28)	69.93 (9.62)	67.97 (9.56)	65.56 (9.66)	63.08 (9.9)	<0.001
Triglycerides (mg/dL)	131.45 (77.63)	141.5 (81.15)	167.14 (100.43)	182.54 (106.53)	189.47 (113.16)	184.16 (105.29)	<0.001
Gender (Male)	20 (30.3)	1043 (45.6)	1872 (54.3)	1239 (52.9)	409 (41.2)	214 (33.6)	<0.001
Region							
North America	27 (40.9)	864 (37.8)	1633 (47.3)	1391 (59.3)	688 (69.3)	520 (81.5)	<0.001
Latin America	2 (3)	37 (1.6)	101 (2.9)	46 (2)	20 (2)	11 (1.7)	0.682
Western Europe	8 (12.1)	451 (19.7)	1036 (30)	691 (29.5)	233 (23.5)	95 (14.9)	0.863
Eastern Europe	1 (1.5)	64 (2.8)	115 (3.3)	66 (2.8)	29 (2.9)	3 (0.5)	0.028
Middle East	0 (0)	26 (1.1)	49 (1.4)	32 (1.4)	6 (0.6)	2 (0.3)	0.008
Asia	14 (21.2)	336 (14.7)	259 (7.5)	66 (2.8)	13 (1.3)	5 (0.8)	<0.001
Japan	14 (21.2)	508 (22.2)	259 (7.5)	52 (2.2)	4 (0.4)	2 (0.3)	<0.001
Medical history							
Current smoker	19 (29.2)	527 (23.9)	655 (19.5)	397 (17.4)	161 (16.7)	101 (16.3)	<0.001
Hypertension	49 (74.2)	1913 (83.7)	3086 (89.4)	2183 (93.1)	955 (96.2)	617 (96.7)	<0.001
Hypercholesterolaemia	41 (62.1)	1723 (75.5)	2787 (80.8)	1933 (82.5)	874 (88)	570 (89.6)	<0.001
TIA							NA
Stroke							NA
MI							NA
Carotid angioplasty/stenting	1 (1.5)	20 (0.9)	25 (0.7)	11 (0.5)	3 (0.3)	1 (0.2)	0.004
Carotid surgery	2 (3.1)	60 (2.7)	92 (2.7)	41 (1.8)	10 (1)	5 (0.8)	<0.001
Congestive heart failure	2 (3.1)	103 (4.6)	162 (4.7)	148 (6.4)	74 (7.6)	63 (10)	<0.001
Aortic valve stenosis	1 (1.6)	47 (2.2)	56 (1.7)	42 (1.9)	19 (2)	7 (1.1)	0.299
Diabetes	42 (63.6)	1494 (65.6)	2438 (70.9)	1861 (79.7)	844 (85)	560 (88.5)	<0.001
Stable angina	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Baseline medication							
Acetyl salicylic acid	21 (32.3)	976 (42.7)	1706 (49.5)	1234 (52.7)	524 (52.9)	327 (51.3)	<0.001
Other antiplatelet agents	9 (13.8)	181 (7.9)	215 (6.3)	124 (5.3)	43 (4.4)	31 (4.9)	<0.001
Other antidiabetic agents	6 (9.2)	299 (13.3)	338 (10)	203 (8.9)	75 (7.9)	47 (7.8)	<0.001

Oral anticoagulants	3 (4.6)	113 (5.1)	184 (5.5)	151 (6.7)	52 (5.4)	46 (7.5)	0.016
β-Blockers	16 (24.6)	563 (24.9)	980 (28.6)	731 (31.4)	322 (32.8)	182 (29)	<0.001
Statins	38 (58.5)	1492 (65.3)	2419 (70.2)	1697 (72.5)	734 (74)	507 (79.6)	<0.001
Other lipid-lowering agent	5 (7.8)	331 (14.5)	576 (16.8)	393 (16.8)	191 (19.4)	110 (17.3)	0.001
Calcium channel blockers	22 (33.8)	824 (36.3)	1190 (34.7)	845 (36.4)	394 (40.2)	207 (33)	0.559
Nitrates/anti-angina agents	3 (4.7)	70 (3.1)	94 (2.8)	64 (2.8)	33 (3.5)	20 (3.2)	0.802
Diuretics	24 (36.9)	759 (33.5)	1503 (43.7)	1251 (53.8)	609 (62)	410 (64.8)	<0.0001
ACE inhibitors	22 (33.8)	814 (36)	1544 (45.1)	1124 (48.6)	490 (50.2)	356 (56.3)	<0.0001
A2RBs	16 (24.6)	656 (29.1)	1040 (30.4)	775 (33.4)	355 (36.3)	229 (36.1)	<0.0001
Other anti-hypertensives	5 (7.7)	202 (8.9)	373 (11)	305 (13.2)	150 (15.4)	83 (13.2)	<0.0001
Peripheral arterial vasodilators	1 (1.6)	82 (3.7)	108 (3.2)	68 (3)	25 (2.6)	17 (2.8)	0.111

Values are given as number (percentage), aside age, BMI, and triglycerides, given as mean ± standard deviation. Percentages are slightly off because of denominator changes due to missing observations in some of the categorical variable.
ACE, angiotensin-converting enzyme; A2RBs, angiotensin 2 receptor blockers; BMI, body mass index; MI, myocardial infarction.

cholesterol, triglycerides, smoking, and serum creatinine levels. Moreover, to assess the relationship between BMI and the outcomes studied according to the use of optimal therapy, two contrasted groups were defined from the secondary prevention cohort: patients on optimal therapy and patients on suboptimal therapy. Hazard ratios (using the normal BMI group as reference) and crude event rates of the various outcomes studied were estimated for each BMI category. The proportional hazards assumption was systematically checked for all Cox models conducted in this study, and values of $P < 0.05$ were considered significant.

Results

Of the 68 236 patients enrolled in the REACH registry, 54 285 ($n = 9779$ in primary prevention and $n = 44\,506$ in secondary prevention) were eligible for inclusion in this analysis. The flowchart is presented in *Figure 1*.

Baseline risk factors

Baseline characteristics are presented according to history of CV events and BMI category in *Tables 1* and *2*. In both primary and secondary CV prevention, a higher BMI was associated with lower age and lower prevalence of current smoking. In secondary prevention, the subgroup of subjects with BMI < 18 kg/m^2 displayed the highest prevalence of current smokers. The male-to-female ratio differed significantly according to BMI: overweight and Grade I obese patients (BMI between 30 and 34.9 kg/m^2) were predominantly males, whereas the proportion of females was similar to (secondary prevention) or higher than (primary prevention) the proportion of males in underweight and severely obese patients.

Use of cardioprotective drugs

The various medications used at baseline are shown in *Tables 1* and *2*. Compared with the underweight but also to the normal weight group, overweight and obese subjects were globally better treated in terms of CVD prevention both in primary and secondary prevention: the highest frequency of use of statins, ACE inhibitors and ARBs, and aspirin and β-blockers was observed in patients with Grade II or Grade III obesity and the lowest frequency in underweight patients. In secondary prevention, optimal therapy was prescribed in 11 448 patients (25.8% of the population), whereas suboptimal therapy (1 or less medication prescribed) was used in 5846 patients (13.2%). The proportion of patients on optimal therapy varied with the BMI class and was 10.1, 18.3, 27.2, 32.8, 36.0, and 32.6% in patients with BMI <18 kg/m^2, 18–24.9 kg/m^2, 25–29.9 kg/m^2, 30–34.9 kg/m^2, 35–39.9 kg/m^2, and ≥ 40 kg/m^2, respectively.

Body mass index and waist circumferences categories and cardiovascular outcomes

A total of 6036 CV (fatal or non-fatal) events and 4706 deaths from any cause, including 2543 CV deaths, occurred in the overall cohort during the 4-year follow-up. In primary prevention, the cumulative events rates were 8.3, 9.1, and 4.3%, respectively, for all-cause mortality, all CV events, and CV mortality. In secondary prevention, these rates were 12.3, 15.6, and 7.6%, respectively. Underweight patients had the highest incidence rate of events for each of the three endpoints examined. Despite the relatively small sample size

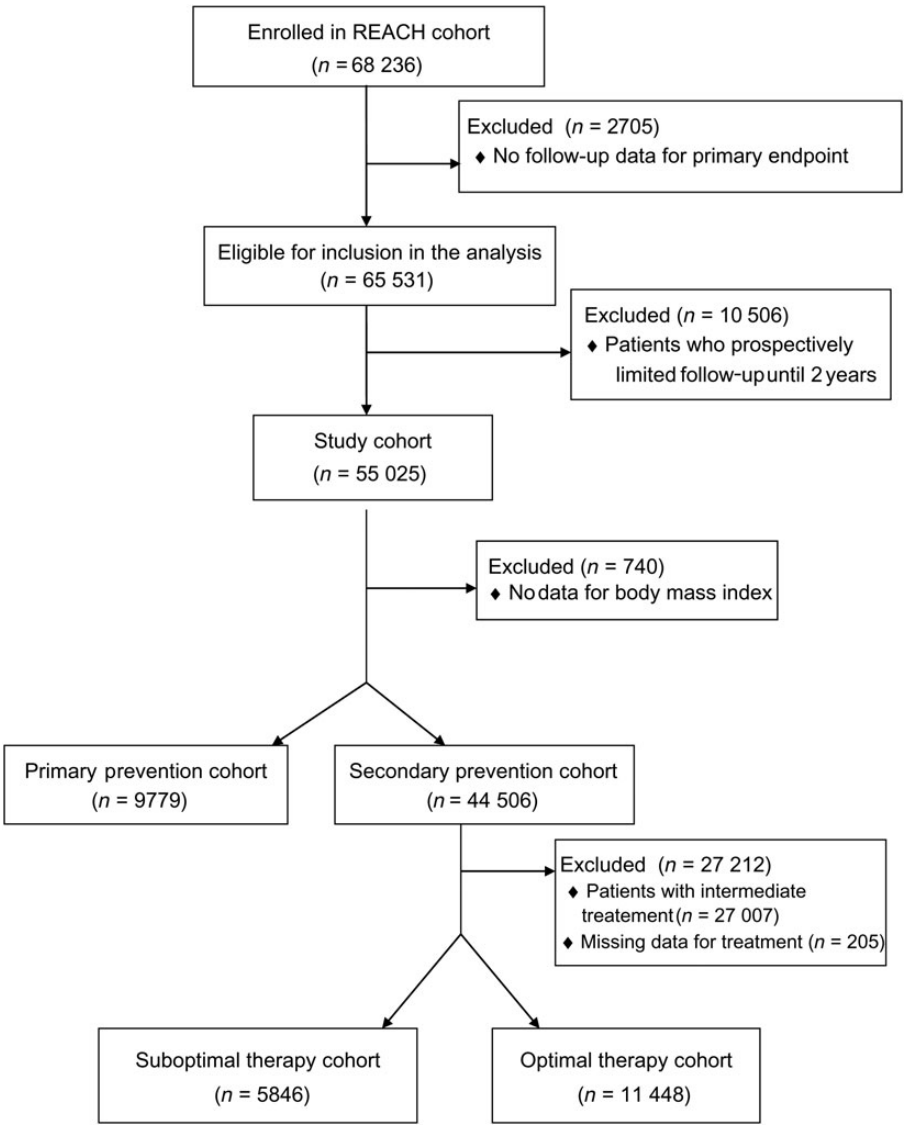

Figure 1 CONSORT flow diagram of study participants.

($n = 66$ in primary prevention; $n = 500$ in secondary prevention) of the underweight group, the risks for CV mortality and CV mortality/myocardial infarction (MI)/stroke were consistently and significantly higher than in the reference group (BMI: 18–24.9 kg/m^2; *Figures 2* and *3*).

In primary and secondary prevention, a reverse J-shaped curve best described the relationship between BMI and the incidence of CVD (CV mortality/MI/stroke), CV mortality, and all-cause mortality (*Figures 2* and *3*). The lowest mortality and CV event rates were observed in either obese or overweight subjects, whereas underweight subjects displayed a markedly increased CV risk. In primary prevention, overweight and Grade I obesity were associated with a reduction of CV events compared with the reference group (*Figures 2A* and *3*). In secondary prevention, compared with the normal weight group, the risk of all-cause mortality, CV mortality, and total CV events was decreased in overweight, Grade I, and Grade II patients, and Grade III obesity was associated with a reduced risk of total CV events (*Figures 2B* and *3*). Additional analyses stratified by sex showed consistent results (see Supplementary material online, *Figures S6* and *S7*). The pattern of the relationship between waist circumference and the incidence of the various outcomes was similar to those of the BMI outcomes relationship (see Supplementary material online, *Figure S8*).

Impact of optimal medical therapy on the body mass index or waist circumference–cardiovascular outcomes relationship

We then assessed the relationship between BMI and outcomes according to the use of optimal therapy for the prevention of CVD. We restricted the study to the patients in secondary prevention, for whom OMT is consensual. As expected, patients on OMT had

Table 2 Baseline characteristics of the secondary prevention cohort by BMI category

BMI classes	Secondary prevention (n = 44 506)						P
	1 (n = 500)	2 (n = 14 038)	3 (n = 18 271)	4 (n = 8139)	5 (n = 2425)	6 (n = 1133)	
Age	72.49 (10.24)	69.82 (10.21)	67.98 (9.93)	66.57 (9.85)	65.22 (9.52)	63.52 (9.29)	<0.001
Triglycerides (mg/dL)	121.67 (76.83)	139.32 (81.92)	159.98 (91.19)	179.62 (105.43)	185.62 (103.28)	185.61 (109.09)	<0.001
Gender (Male)	247 (49.4)	9293 (66.2)	13 087 (71.6)	5449 (67)	1389 (57.3)	572 (50.5)	<0.001
Region							
North America	129 (25.8)	3499 (24.9)	5797 (31.7)	3555 (43.7)	1397 (57.6)	862 (76.1)	<0.001
Latin America	17 (3.4)	451 (3.2)	675 (3.7)	236 (2.9)	58 (2.4)	20 (1.8)	0.001
Western Europe	57 (11.4)	3512 (25)	6065 (33.2)	2577 (31.7)	613 (25.3)	146 (12.9)	0.020
Eastern Europe	16 (3.2)	1320 (9.4)	2482 (13.6)	1195 (14.7)	265 (10.9)	64 (5.6)	<0.001
Middle East	1 (0.2)	155 (1.1)	297 (1.6)	135 (1.7)	44 (1.8)	15 (1.3)	<0.001
Asia	142 (28.4)	2383 (17)	1723 (9.4)	305 (3.7)	40 (1.6)	24 (2.1)	<0.001
Japan	138 (27.6)	2718 (19.4)	1232 (6.7)	136 (1.7)	8 (0.3)	2 (0.2)	<0.001
Medical history							
Current smoker	119 (24.5)	2275 (16.7)	2582 (14.6)	1025 (13)	312 (13.3)	138 (12.5)	<0.001
Hypertension	354 (70.8)	10 303 (73.4)	14 547 (79.6)	7012 (86.2)	2203 (90.8)	1032 (91.1)	<0.001
Hypercholesterolaemia	211 (42.2)	8405 (59.9)	13 030 (71.4)	6128 (75.4)	1871 (77.3)	911 (80.5)	<0.001
TIA	75 (15.4)	2163 (15.8)	2847 (15.9)	1248 (15.6)	389 (16.4)	181 (16.5)	0.0539
Stroke	205 (41.6)	4335 (31.2)	4381 (24.2)	1727 (21.4)	492 (20.5)	208 (18.5)	<0.001
MI	128 (25.8)	4710 (34)	7266 (40.3)	3272 (40.7)	990 (41.2)	433 (39)	<0.001
Carotid angioplasty/stenting	11 (2.2)	358 (2.6)	486 (2.7)	241 (3)	80 (3.3)	37 (3.3)	0.005
Carotid surgery	23 (4.6)	671 (4.8)	859 (4.7)	394 (4.9)	101 (4.2)	50 (4.5)	0.0459
Congestive heart failure	81 (16.4)	1836 (13.3)	2625 (14.6)	1417 (17.7)	532 (22.3)	306 (27.6)	<0.001
Aortic valve stenosis	10 (2.1)	419 (3.1)	602 (3.5)	293 (3.8)	75 (3.2)	40 (3.7)	0.034
Diabetes	129 (25.9)	4167 (29.9)	6323 (34.9)	3777 (46.7)	1355 (56.2)	740 (65.8)	<0.001
Stable angina	148 (29.8)	4450 (32.2)	6759 (37.5)	3371 (42)	963 (40.2)	453 (40.2)	<0.001
Baseline medication							
Acetyl salicylic acid	300 (60.1)	9559 (68.2)	13 287 (72.8)	6021 (74.1)	1785 (73.7)	819 (72.4)	<0.001
Other antiplatelet agents	174 (34.8)	4436 (31.7)	5244 (28.9)	2098 (25.9)	589 (24.5)	282 (25)	<0.001
Other antidiabetic agents	25 (5)	620 (4.4)	698 (3.9)	375 (4.7)	107 (4.5)	60 (5.5)	0.0217
Oral anticoagulants	67 (13.9)	1808 (13.2)	2329 (13.1)	1058 (13.4)	361 (15.5)	159 (14.7)	0.020
β-Blockers	151 (30.3)	5933 (42.4)	9821 (53.9)	4835 (59.6)	1462 (60.6)	660 (58.5)	<0.001
Statins	216 (43.2)	8407 (59.9)	12 861 (70.5)	5979 (73.5)	1814 (74.9)	858 (75.9)	<0.001
Other lipid-lowering agent	27 (5.4)	1213 (8.7)	1965 (10.8)	1070 (13.2)	364 (15.1)	211 (18.7)	<0.001

Continued

Table 2 *Continued*

BMI classes	Secondary prevention ($n = 44\,506$)						P
	1 ($n = 500$)	2 ($n = 14\,038$)	3 ($n = 18\,271$)	4 ($n = 8139$)	5 ($n = 2425$)	6 ($n = 1133$)	
Calcium channel blockers	178 (35.6)	4959 (35.4)	6094 (33.5)	2735 (33.8)	869 (36.2)	396 (35.1)	0.342
Nitrates/ anti-angina agents	129 (26.1)	3916 (28.3)	5324 (29.5)	2403 (30)	709 (30)	329 (29.6)	0.004
Diuretics	131 (26.3)	4117 (29.4)	6833 (37.5)	3968 (48.9)	1475 (61.1)	720 (63.8)	<0.001
ACE inhibitors	161 (32.3)	5323 (38)	8470 (46.6)	4238 (52.4)	1319 (54.8)	584 (51.7)	<0.001
A2RBs	84 (16.9)	2710 (19.4)	3666 (20.2)	1743 (21.6)	593 (24.6)	298 (26.5)	<0.001
Other anti-hypertensives	34 (6.8)	993 (7.1)	1520 (8.4)	837 (10.4)	292 (12.2)	159 (14.2)	<0.001
Peripheral vasodilators	52 (10.5)	1164 (8.4)	1409 (7.8)	587 (7.4)	140 (5.9)	62 (5.6)	<0.001

Values are given as number (percentage), aside age, BMI, and triglycerides, given as mean ± standard deviation. Percentages are slightly off because of denominator changes due to missing observations in some of the categorical variable.
ACE, angiotensin-converting enzyme; A2RBs, angiotensin 2 receptor blockers; BMI, body mass index; MI, myocardial infarction.

better outcomes (*Figures 4* and *5*). The reverse J-shaped BMI–CV relationship persisted markedly in patients on OMT: overweight and Grade I obese patients still displayed protection against all-cause mortality, CV endpoints (CV mortality/MI/stroke), and CV mortality (*Figures 4* and *5A*). In addition, Grade II obesity was associated with a significant reduction in all-cause mortality, whereas Grade III obesity tended to be associated with decreased mortality. In contrast, the BMI–CV relationship was considerably attenuated in patients on suboptimal therapy (*Figures 4* and *5B*). Underweight remained significantly associated with an increased risk of mortality and CV events. However, overweight and obesity were no longer associated with any protection. The interaction between BMI and quality of treatment (optimal or suboptimal) was significant for overweight patients for the three outcomes. Other interactions were not statistically significant (data not shown).

Similar results were obtained when considering waist circumference rather than BMI categories in the sensitivity analysis (see Supplementary material online, *Figure S9*). Additional analyses stratified by sex showed consistent results although statistically less significant, due to a lower statistical power (see Supplementary material online, *Figures S10* and *S11*).

Discussion

In this study, obese patients did not display a clear excess risk of morbi-mortality in a population of 54 285 subjects at high risk for CVD, recruited worldwide. In the overall population, a high BMI was associated with the best prognosis. Further analyses examined potential methodological biases. First, we separately examined patients in primary and secondary CV prevention and observed that CV events were less frequent among obese patients in both groups. Obesity was also associated with more frequent use of cardioprotective drugs and OMT. Most importantly, the apparent protection associated with obesity persisted among patients receiving optimal secondary prevention therapy. Surprisingly, this paradoxical cardioprotection was attenuated in the population receiving suboptimal therapy. Our results extend information from a previous analysis of a subgroup from the REACH registry,[22] restricted to diabetic participants, and 2-year outcomes.

The apparent protection conferred by obesity is not limited to populations with heterogeneous cardiovascular risk

Most previous studies in patients at high CV risk or with CHD support the obesity paradox, described by a U-shaped relationship between BMI and CV events. A meta-analysis[5] in patients with CHD concluded on a decreased relative risk for total mortality and CV mortality in overweight subjects compared with subjects with normal BMI. However, in contrast with our results, the CV risk of patients with BMI between 30 and 35 kg/m^2 did not differ from that of normal weight patients. One limitation of the numerous studies reporting the obesity paradox is the heterogeneity of study populations, including both patients simply at high CV risk and others with overt CVD. Since it has previously been pointed out that the relationship between obesity and mortality varies according to health status, such heterogeneity may in theory account for the obesity

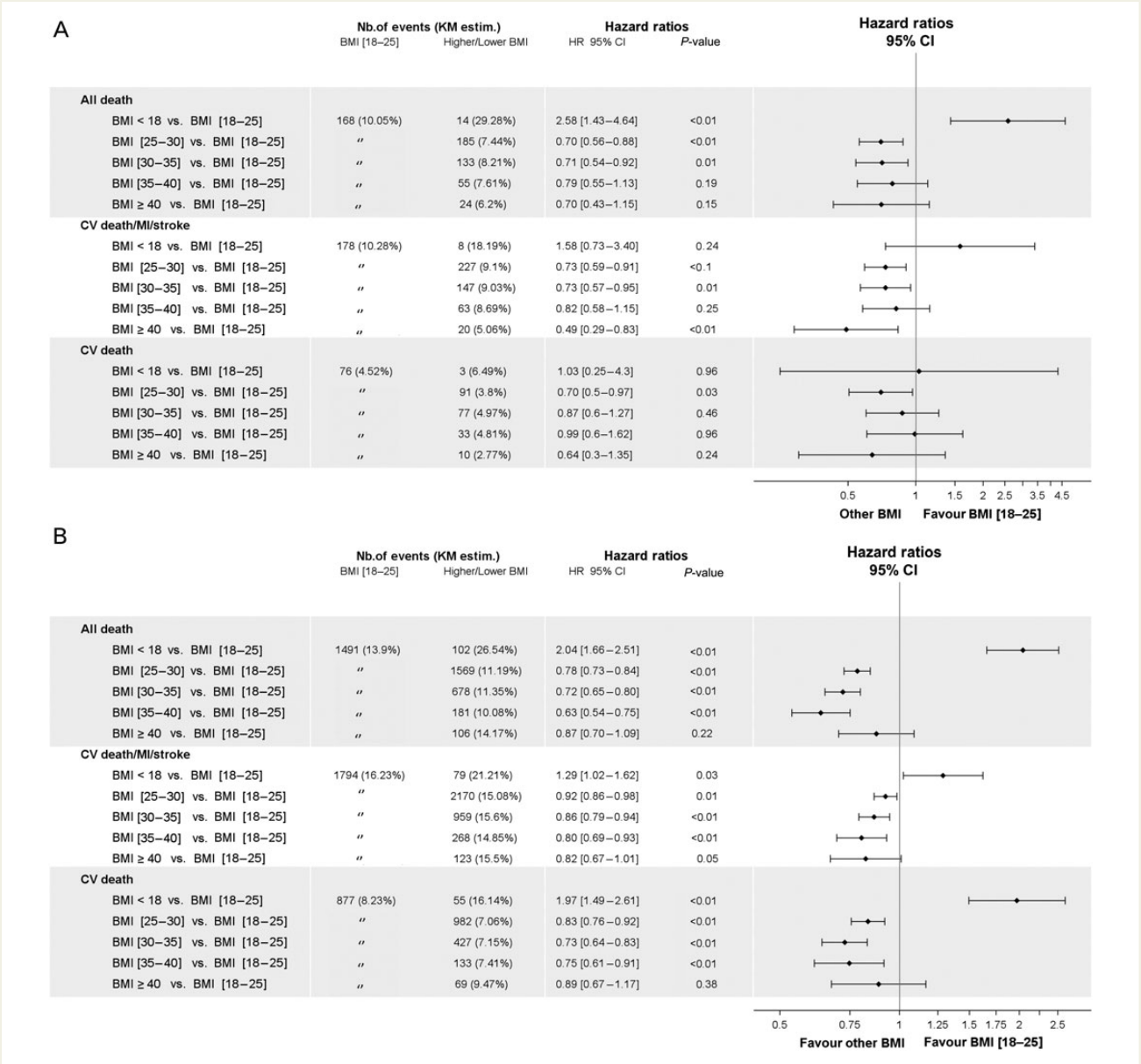

Figure 2 Risks of outcomes in the primary (*A*) and secondary (*B*) prevention cohorts for patients in various body mass index groups compared with patients in the 'normal body mass index' group. The hazard ratios and 95% confidence intervals are displayed on a logarithmic scale. CV, cardiovascular; BMI, body mass index; MI, myocardial infarction; HR, hazards ratio; CI, confidence interval.

paradox.[23] In the present study, we distinguished patients in primary and secondary CV prevention and observed a consistent CV protective effect of obesity in both groups. This observation minimizes the risk of reverse causality bias (i.e. patients in secondary prevention have lower BMI because of their history of CVD).

Obese patients are more likely to receive optimal therapy

One hypothesis proposed to explain the apparent protective effect of overweight and obesity is confounding related to differences in the use or doses of evidence-based medications (i.e. statins, aspirin, ACE inhibitors or ARBs, and β-blockers). In REACH, these agents were each more frequently used in obese compared with normal weight subjects, both in primary and secondary prevention (*Table 1*). This is in accordance with the results of previous smaller studies.[11,12,15,24] To our knowledge, no study has previously described the quality of treatment in patients at high CV risk, including patients with all degrees of obesity. In the present study, there was a relatively low proportion of patients on OMT, and specifically a lower use of statins compared with other secondary prevention studies,[24] possibly because of the global nature of enrolment in REACH.

Another novelty of this analysis is that the size of the REACH cohort allowed a stratified analysis according to the quality of therapy (optimal vs. suboptimal), which found that protective effect of obesity persists in patients on OMT, contrasting with a prior smaller

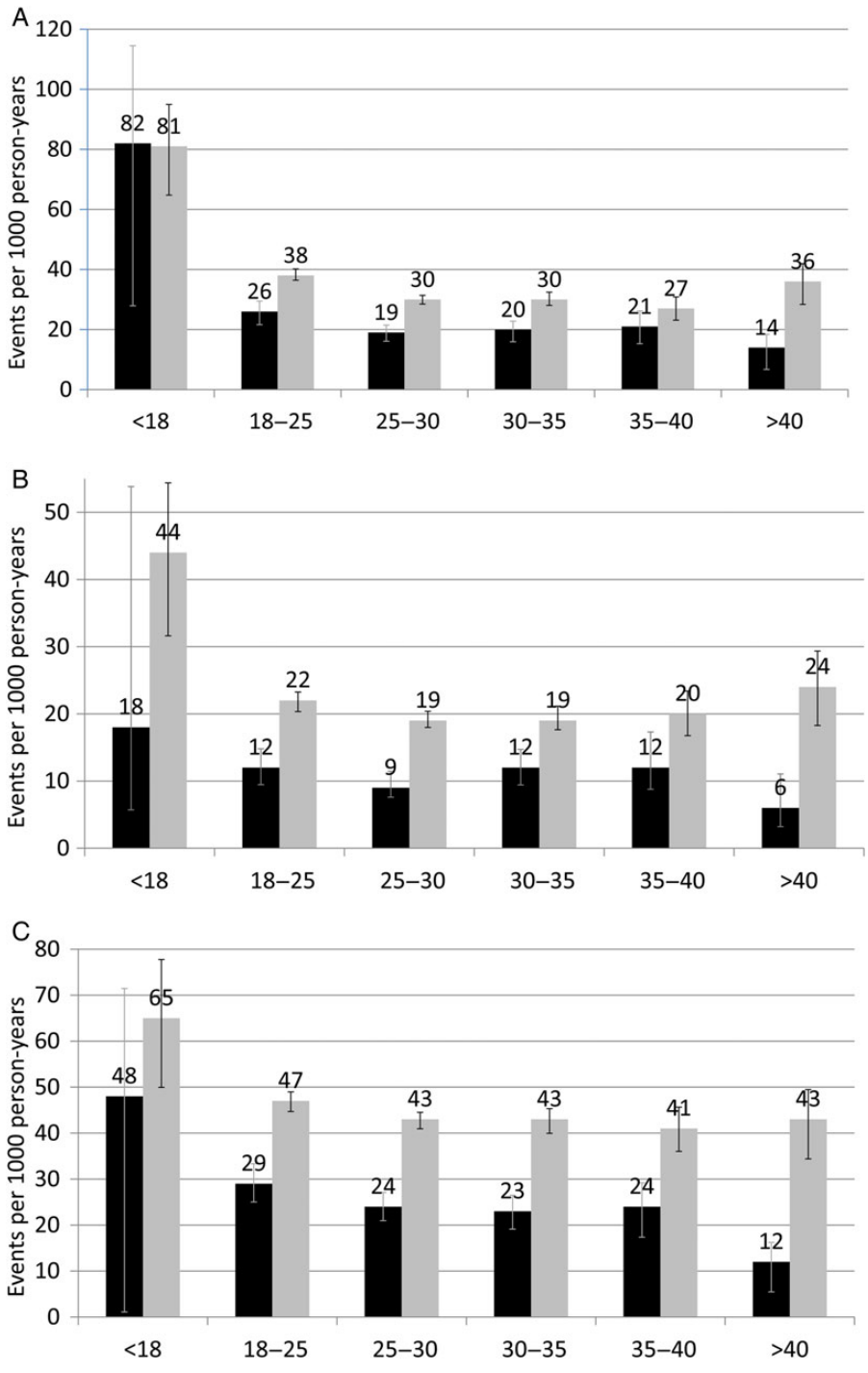

Figure 3 Crude incidence rates by body mass index categories in the primary prevention (black) and secondary prevention (grey) cohorts: all-cause mortality (*A*), cardiovascular mortality (*B*), and cardiovascular mortality/myocardial infarction/stroke composite endpoint (*C*). Error bars indicate 95% confidence intervals for rates.

study[11] (but the latter used regression and therefore assumed that risk is evenly distributed in the controlled factor).

Finally, the hypothesis of differences between men and women for the obesity paradox is not supported by our additional stratified analyses by sex, confirming prior results.[25] However, this hypothesis cannot be totally excluded, and further investigation of the interaction between body composition and gender in CVD and mortality outcomes is warranted.

Explanations of the obesity paradox

Several hypothetical explanations have been proposed for the obesity paradox, which could also explain the reverse J-shaped

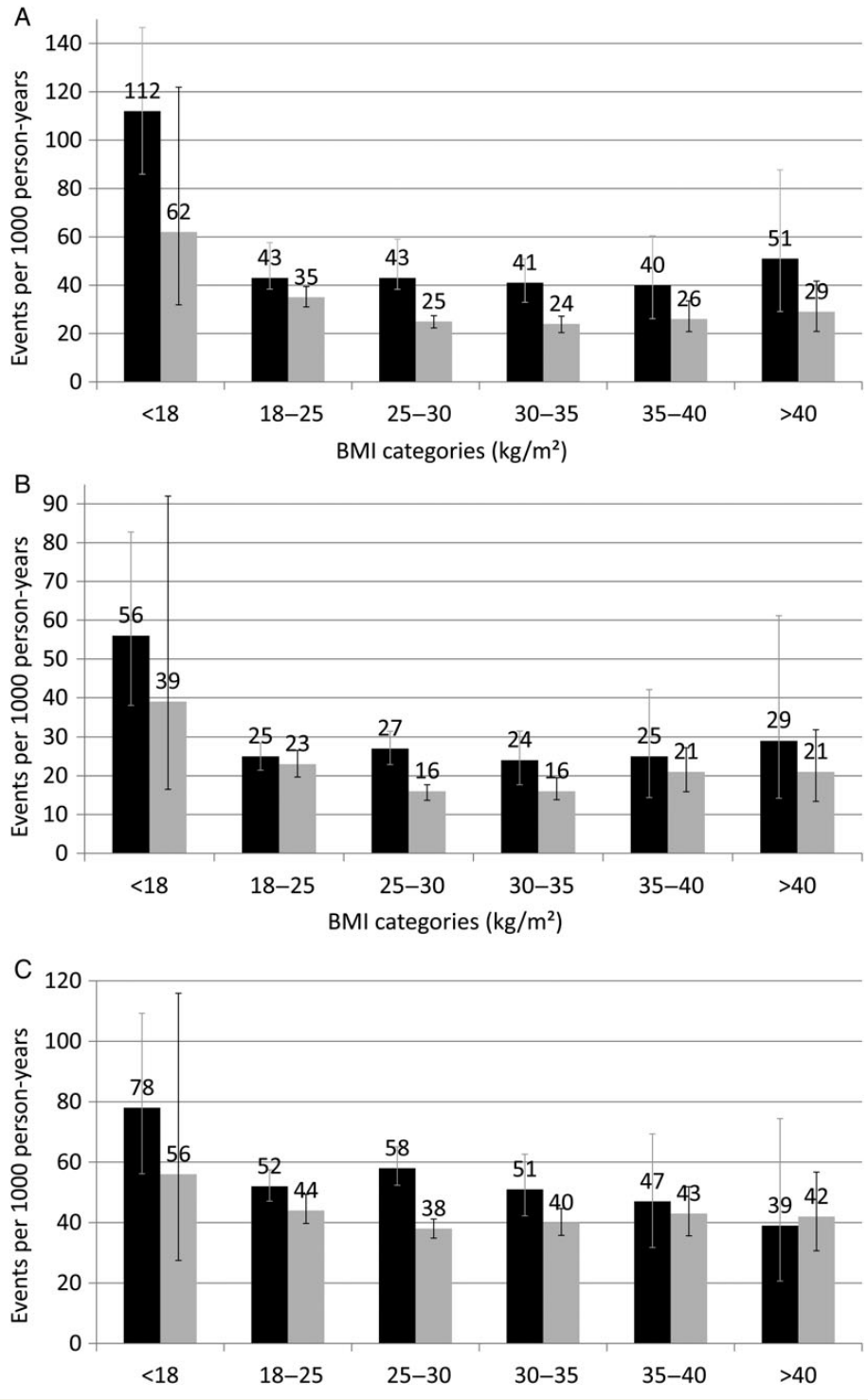

Figure 4 Crude incidence rates in the secondary prevention cohort by body mass index category according to optimal (grey) vs. suboptimal (black) therapy for all-cause mortality (*A*), cardiovascular mortality (*B*), cardiovascular mortality/myocardial infarction/stroke composite endpoint (*C*). Error bars indicate 95% confidence intervals for rates.

relationship between BMI and CVD. First, BMI reflects total adiposity more than central adiposity. A lower BMI is not only a marker of a lower amount of visceral fat but also a marker of a lower peripheral adiposity which confers CV and metabolic benefits due to the secretion of insulin-sensitizing and anti-inflammatory adiponectin molecules. In addition, BMI does not differentiate lean body mass and fat mass, a critical potential confounding factor, as indicated above, as higher event rates in the high BMI categories could be

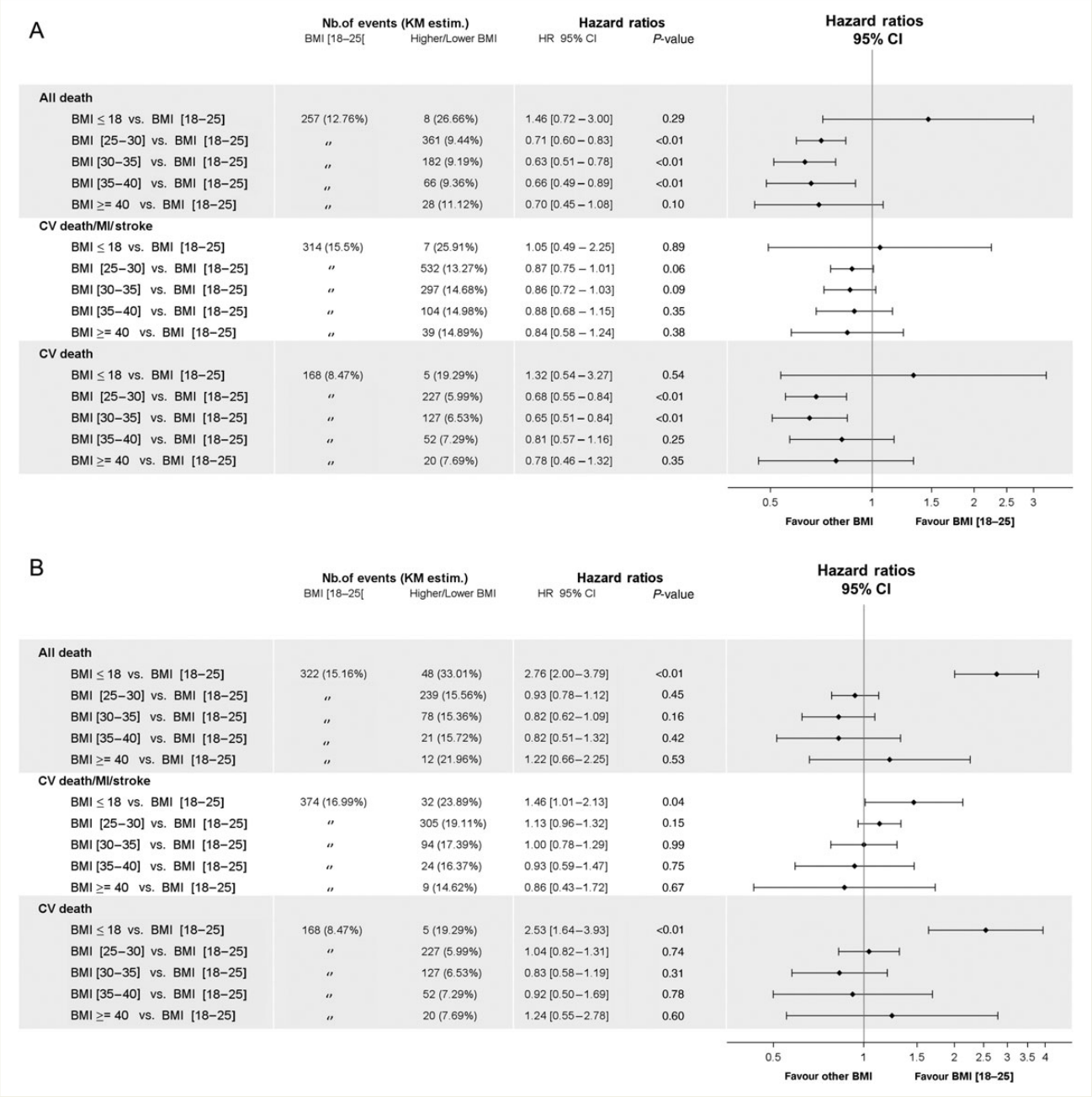

Figure 5 Risks of outcomes in the secondary prevention cohort for patients with optimal therapy (*A*) and suboptimal therapy (*B*), in various body mass index groups compared with patients in the reference group (18 kg/m^2 < body mass index < 25 kg/m^2). The hazard ratios and 95% confidence intervals are displayed on a logarithmic scale. CV, cardiovascular; BMI, body mass index; MI, myocardial infarction; HR, hazards ratio; CI, confidence interval.

explained by sarcopenic obesity, characterized by low muscle mass. In patients with chronic heart failure, BMI misclassified body fat status in 41% of patients.[26] Several authors have recently proposed the concept of a 'lean paradox' rather than an 'obesity paradox'.[27] We observed similar, although somewhat attenuated, relationships between waist circumference and outcomes and those observed with BMI, but waist circumference is not a good surrogate for visceral adiposity in Grade II+ obesity. Apart from the mechanisms mentioned above, the obesity paradox might simply be the result of collider stratification, a well-known source of selection bias in epidemiology.[28] A special case of this bias is called the 'recurrence bias': in patients who have already experienced a CV event, a higher prevalence of the four modifiable major CV risk factors (i.e. history of high cholesterol levels, smoking, hypertension, and diabetes) may be observed in lean patients compared with obese patients. Obesity, a minor CV risk for CVD recurrence compared with other major

CV factors, may therefore appear to be a protective factor for recurrence of CV events. However, in our study, the reverse J-shaped relationship was demonstrated not only in secondary prevention but also in primary prevention. The 'collider bias' is therefore unlikely to fully account for the apparent protective effect of obesity on CVD. Interestingly, in the subset of diabetic participants,[22] waist circumference showed only a trend for non-fatal MI and all CV events. The power of the current analysis was higher due to longer follow-up (4 vs. 2 years) and a larger population. In addition, given the high prevalence of abdominal adiposity among diabetics, it may carry less prognostic information than in the general population.

The protection conferred by obesity is attenuated in patients on suboptimal therapy

Analysis of the interaction between BMI and quality of therapy revealed that suboptimal medical therapy was associated with decreased apparent CV protection of overweight subjects. Quality of therapy may be a marker for co-morbidities or risk factors unevenly distributed between the overweight/obesity and reference groups, such as lifestyle, including physical activity, which is a major determinant of body composition.[29] Altogether, these data may explain why the obesity paradox persists when the population is limited to patients on OMT (BMI would not be a reliable marker of fat mass in this case, and low BMI may be due to sarcopenia), and why the apparent protection conferred by obesity does not persist in patients on suboptimal therapy (BMI might be a more accurate marker of harmful fat mass in these patients).

Strengths and limitations of the study

The international REACH registry has included a large population of 54 285 subjects with a follow-up of up to 4 years and is likely to be a representative of many ethnicities or country backgrounds. In addition, there was a detailed collection of risk factors and medical management. However, the present analysis also has limitations. First, changes in body weight after the index event were not recorded, making it impossible to assess the potential effects of weight change (intentional or unintentional) on prognosis. There was no information on some important confounders such as physical activity or fitness status,[30–34] diet (including alcohol intake), or inflammation. Another limitation is the lack of information regarding the reason of thinness in the group with BMI <18 kg/m^2, which is probably a heterogeneous group of patients. Further studies are needed to fully characterize the various reasons for and the CV implications of being underweight.

Clinical perspective

The 'obesity paradox' (patients with a higher baseline BMI have a better outcome) is often used to argue against recommending weight loss in obese patients. As this approach is highly counter-intuitive, the observed phenomenon is described as 'paradoxical'. This paradox is based on the assumption that, for a given patient, weight loss is identical to the change from the high BMI group to a lower BMI group, but this assumption is incorrect. For a given patient, the baseline BMI group cannot be modified. However, these observations remain useful to clinicians as clinical decisions are based on a single patient approach, and, in the light of the current and previous observations, the clinician is aware that (i) lean and very obese patients are at higher risk, and normal weight and overweight patients are at lower risk, so risk prediction on a single patient basis is more accurate, and (ii) OMT, although necessary, is not sufficient to reduce the higher risk of the extreme BMI groups.

Conclusions

These results are consistent with a cardioprotective effect of overweight and obesity in both primary and secondary prevention. These results argue against a confounding role of OMT to explain the better outcome in patients with a history of CV events. Further studies of the relationship between BMI and CVD are required with special focus on the effect of fatness vs. fitness on CV risk.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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