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Obesity, metabolic health and clinical outcomes after incident cardiovascular disease: A nationwide population-based cohort study

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Abstract

Background The association between metabolic syndrome and increased cardiovascular disease (CVD) risk is well-established. However, in patients with incident CVD, the relationship between obesity, metabolic health, and subsequent CVD and mortality outcomes are less well-established. This study investigated the association between body mass index (BMI), metabolic health and the risk of subsequent cardiovascular mortality and morbidity outcomes in patients with incident CVD events.

Methods This cohort study identified 130 685 patients from the nationwide Clinical Practice Research Datalink (CPRD GOLD) and Hospital Episode Statistics (HES) databases in the United Kingdom. Patients were ≥18 years with incident CVD [coronary heart disease (CHD), stroke, or peripheral vascular disease (PVD)] between 1 January 1998 and 31 December 2017. BMI (in kg/m^2) was categorized as underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9) and obese (≥30). Within each BMI category, patients were grouped by increasing count of 1, 2 or 3 metabolic risk factors [RF] (dyslipidaemia, diabetes mellitus and hypertension) and were regarded as metabolically unhealthy while absence of these factors was considered metabolically healthy (MH). Multivariable Cox regression was used to assess the risk (hazard ratio with 95% confidence interval) of subsequent outcomes (non-fatal CHD, stroke, PVD, incident heart failure, CVD-mortality and all-cause mortality) in BMI subgroups with incremental count of metabolic RFs.

Results During a median follow-up of 13.0 years, a higher BMI was associated with reduced risk for stroke, PVD, CVD-mortality and all-cause mortality within each metabolic risk category, while increasing metabolic RFs within each BMI subgroup accounted for increasing risks. When compared with patients with normal BMI and no RF, CVD-mortality risk in overweight patients with no RF was 0.76 (0.70–0.84), and in obese patients with no RF was 0.85 (0.76–0.96). The respective risk for all-cause mortality in patients with overweight and no RF was 0.69 (0.65–0.72), and in obese patients with no RF was 0.75 (0.70–0.79). Subsequent outcomes of stroke and PVD showed similar trends. In contrast, the risk of subsequent non-fatal CHD events and incident HF increased with higher BMI and with incremental metabolic risk factors within each BMI category. Underweight was constantly associated with increased risk for all outcomes regardless of the presence of metabolic RFs except for non-fatal CHD events.

Conclusions In patients with incident CVD, overweight and obesity were related to a more favourable prognosis for subsequent stroke, PVD and mortality (CVD-related and all-cause) irrespective of the presence of other metabolic risk factors.

Keywords Body mass index; Cardiovascular disease; Electronic health records; Metabolically healthy obesity; Obesity paradox; Real-world evidence

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Introduction

Metabolic syndrome refers to a cluster of interrelated metabolic abnormalities mostly including generalized obesity, glucose intolerance, arterial hypertension and dyslipidaemia.[1] It is estimated that about 20–30% of the adult population in most countries can be classified as having metabolic syndrome.[2] The increased risk of cardiovascular disease (CVD) outcomes associated with metabolic syndrome is well established.[3]

In the healthy population, the presence of excessive body weight is generally recognized as a key marker of metabolic risk and accordingly, weight reduction in overweight and obese subjects is widely regarded as an important intervention target for primary prevention to avoid cardiovascular disease. However, in patients with established incident cardiovascular disease, the interplay between obesity, metabolic health (as assessed by the absence of the other components of the metabolic syndrome, i.e., diabetes mellitus, arterial hypertension and dyslipidaemia) and subsequent cardiovascular outcomes is less clear. Increasing evidence suggests that in a range of cardiovascular diseases, once the disease is established and survival *with the existing disease* is the foremost health concern, overweight and mild obesity may not carry an additional risk but are, in fact, related to a better outcome.[4] This observation seemingly contradicts the characteristic of obesity as a classical metabolic risk factor. Using a nationwide population-based cohort in the United Kingdom, this study aimed to investigate the association between body weight, the general status of metabolic health and the risk of subsequent cardiovascular mortality and morbidity outcomes in patients with incident CVD events. Besides wide-ranging clinical and behavioural characteristics also comprehensive social and socioeconomic cofactors were taken into account in these analyses.

Methods

Data source

This prospective population-based cohort study used the UK Clinical Practice Research Datalink (CPRD) GOLD database of anonymized longitudinal primary care electronic health records (EHR).[5] Individuals included in the CPRD GOLD database, from a network of general practices across the United Kingdom, are representative of the UK general population in terms of sex, age and ethnicity,[5] thereby validating CPRD GOLD for epidemiological research. The primary care EHRs (CPRD GOLD) were linked to secondary care hospitalisation data [Hospital Episode Statistics (HES)],[6] national mortality data [Office for National Statistics (ONS)][7] and social deprivation data [Index of Multiple Deprivation (IMD) 2015].[8] This study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (Protocol number 19_023R).

Study population

We identified a cohort of individuals with incident non-fatal cardiovascular events [defined as an incident diagnosis of either coronary heart disease (CHD), stroke, or peripheral vascular disease (PVD)] in either primary care (CPRD GOLD) or secondary care (HES) between 1 January 1998 and 31 December 2017. Individuals were free of CVD prior to the index event. Individuals were followed from the date of incident CVD diagnosis until they developed a major adverse cardiovascular event, died, ceased contributing data, or end of data collection on 22 August 2019. The study population thus comprised individuals with incident yet non-fatal cardiovascular events because the purpose of the study was to assess the association between BMI and metabolic health and subsequent outcomes in individuals living with established CV disease.

Cohort demographics and baseline characteristics

Age was defined at the time of the incident CVD event. Ethnicity was categorized into six groups: Asian, Black, Mixed, Other, White and unknown.[9] The socioeconomic status of all subjects was assessed using the English Index of Multiple Deprivation (IMD) 2015.[8] The IMD is the UK government's official measure to comprehensively assess relative deprivation in the United Kingdom. It uses 37 indicators across seven domains (including income, employment and education) to rank 32 844 geographical regions ('Lowest Super Output Areas' containing an average of 1500 people or 650 households), by relative deprivation.[10] Details about each underlying indicator included in the domains are provided in Box S1. The calculated weighted mean, based on the residential postcode of the patient, offers a single score to describe the socioeconomic status as a function of deprivation categorized into quintiles (quintile 1 = least deprived group to quintile 5 = most deprived group). Medication prescriptions at baseline were defined as a prescription within 12 months before any incident CVD event. All other co-morbidities were defined based on the latest record before incident CVD events.

Exposure

Body mass index (BMI) was recorded within 24 months before incident CVD in all patients and was categorized according to the WHO criteria as underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2) and obesity (BMI $\geq$30.0 kg/m^2).[11] Meta-

bolic health status was defined according to the presence of the three other main components of the metabolic syndrome (i.e., arterial hypertension, dyslipidaemia or diabetes mellitus) and was quantified by the cumulative count of metabolic risk factors (0, 1, 2 and 3).[12] The absence of any of these metabolic risk factors was considered as metabolically healthy regardless of BMI. Combining BMI categories and the counts of metabolic factors, patients were categorized into a 4 × 4 matrix of 16 BMI–metabolic health phenotypes. Patients with normal weight and metabolically healthy (i.e., no metabolic risk factors) were used as the reference group.

Endpoints

Individual outcomes of time to the first new onset of fatal and non-fatal event was assessed. Non-fatal outcomes included CHD events, stroke, PVD and heart failure; fatal outcome was assessed for cardiovascular mortality and all-cause mortality.

The study cohort and outcomes were identified from CPRD using Read codes, from HES using International Classification of Diseases, tenth revision (ICD-10) codes and Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) revision 4.6 for procedure codes. All code lists used are available for download from www.caliberresearch.org/portal/.[13]

Statistical analysis

Kruskal-Wallis test for continuous data and the chi-squared test for categorical data were used to compare baseline characteristics between BMI categories. Event rates between the BMI and metabolic state phenotypes were analysed by multivariable Cox regression models using the category of normal BMI and metabolically healthy as a reference. Hazard ratios (HR) and 95% confidence intervals (95% CI) for the outcomes according to BMI-metabolic state categories were calculated in Cox regression in 3 different models: Model 1 was unadjusted and model 2 was adjusted for age, sex, ethnicity, current smoker status, diagnosis of atrial fibrillation, cancer, chronic kidney disease, chronic obstructive pulmonary disease and heart failure. Model 3, the fully adjusted model used all factors of model 2 and additionally accounted for socioeconomic status (IMD), diagnosis of an alcohol problem, alcoholic liver disease, dementia, erectile dysfunction, family history of hyperlipidaemia, family history of CVD, severe mental illness, transient ischaemic attack, prescription ofantihypertensive, anti-arrhythmic, anti-coagulants, anti-diabetics, anti-platelets, and potency of prescribed statin. Restricted cubic spline with 3–5 knots (lowest Akaike information criterion) was also used for the non-linear relationship between BMI and outcomes. All statistical analyses were performed using Stata SE version 17 (StataCorp LP). An alpha level of 0.05 was used for all analyses to define statistical significance.

Results

Characteristics of the cohort

There was a total of 280 081 individual patients aged 18 years and older with an incident, non-fatal CVD event recorded between 1998 and 2017 in CPRD GOLD and HES. A total of 130 685 (46.7%) patients with baseline BMI records were included in this study and were grouped into BMI categories (Figure 1, Table S1). The median follow-up for the study cohort was 13.0 years (IQR: 8.2–17.0 years).

The median age for the study cohort was 71 years (IQR: 61–79 years) with 61 533 (47.1%) of the cohort being women. The baseline demographic and socioeconomic factors differed significantly between both the BMI categories (Table 1) and metabolic health groups (Table 2). The patients with elevated body weight (overweight and obese) generally had a greater number of metabolic risk factors and co-morbid conditions at baseline (Table 1, Figure 1).

Clinical outcomes

During the follow-up period, there were 39 063 (29.9%) patients who had a subsequent CHD event, 18 614 (14.2%) a stroke event, 6762 (5.2%) PVD event, 7712 (5.9%) a heart failure event, 9619 (7.4%) died from a CVD-related cause, and 28 736 (22.0%) died from any cause. Figure 2 (central illustration/graphical abstract) depicts the 16 BMI – metabolic state phenotypes and the relative risk of subsequent cardiovascular morbidity and mortality outcomes, with normal BMI and metabolically healthy group as the reference group. All outcome variables were evaluated from two perspectives of (a) comparison between the BMI categories of patients with a similar count of metabolic risk factors and (b) a comparison of incremental metabolic risk factors within BMI categories.

Coronary heart disease and heart failure

For outcomes CHD and HF, a direct association of BMI and event risk was observed: (a) Patients with higher BMI, irrespective of the number of metabolic risk factors, were at a higher risk of subsequent events of CHD or incident HF. (b) Within each BMI category the risk of CHD or HF events increased with incremental count of metabolic risk factors (Figure 2 and Tables S2 and S3). The finding held true in unadjusted analysis and in both multivariable-adjusted models (Tables S2 and S3).

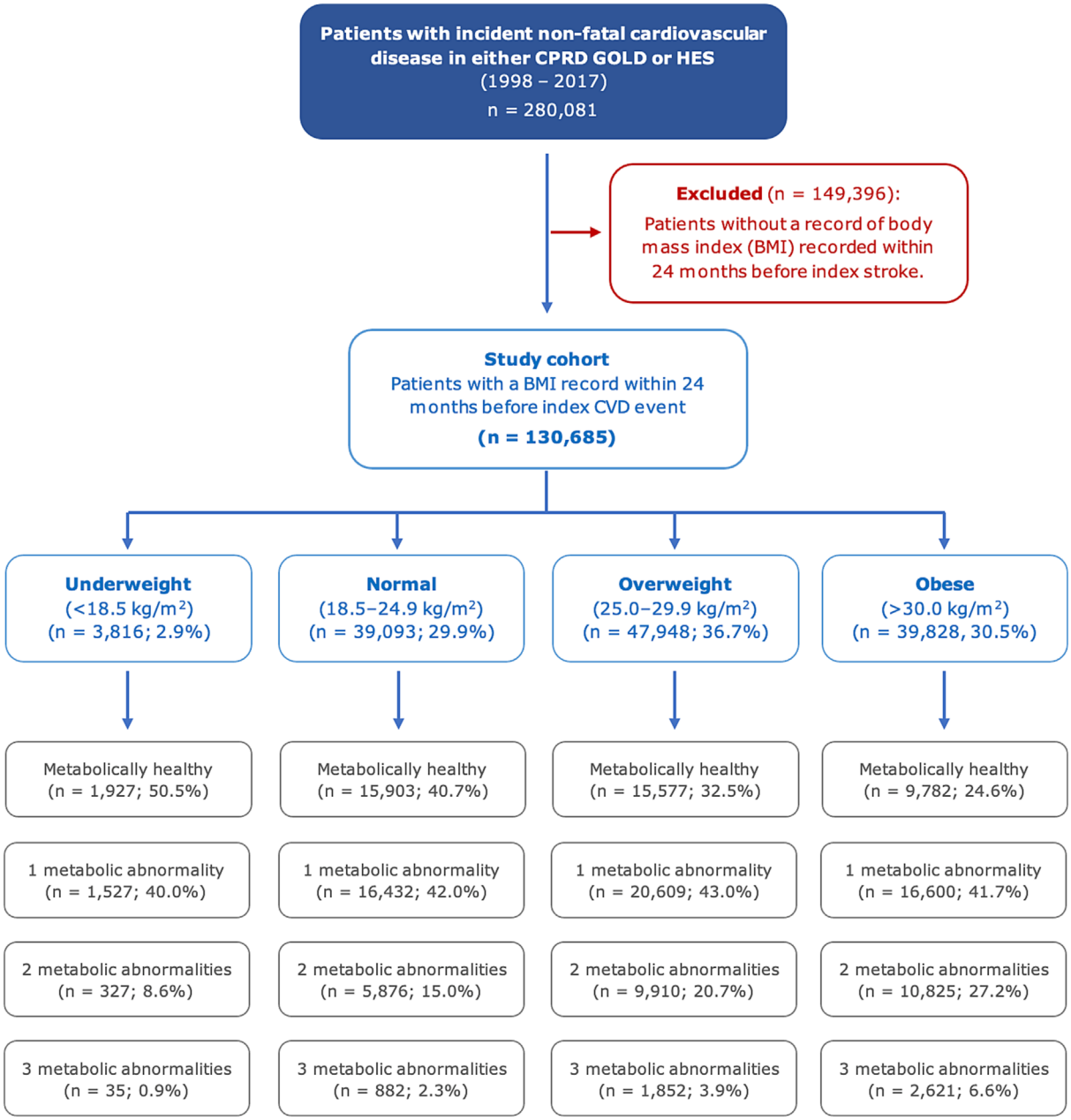

Figure 1 Study flow diagram.

Stroke

For the outcome of stroke, an inverse association between BMI and event risk was observed. (a) Higher BMI was associated with a lower risk of subsequent stroke events and the same pattern was observed within each subgroup of 0, 1, 2 or 3 metabolic risk factors (Figure 2 and Table S4). (b) Within each BMI category additional metabolic risk factors were not associated with increased stroke risk. The hazard in comparison with normal BMI and metabolically healthy patients was in multivariable-adjusted analysis (Model 2) for overweight and metabolically healthy: HR 0.89 (95% CI 0.84–0.94); overweight with 1 metabolic risk factor: HR 0.90 (95% CI 0.86–0.95); overweight with 2 metabolic risk factor: HR 0.79 (95% CI 0.73–0.84); overweight with 3 metabolic risk factor: HR 0.74 (95% CI 0.64–0.84); obese and metabolically healthy: HR 0.82 (95% CI 0.76–0.88); obese with 1 metabolic risk factor: HR 0.84 (95% CI 0.79–0.89); obese with 2 metabolic risk factor: HR 0.79 (95% CI 0.74–0.85); obese with 3 metabolic risk factor: HR 0.72 (95% CI 0.64–0.82, Figure 2 and Table S4). In turn, underweight patients showed increased stroke

Table 1 Characteristics of the study cohort at the time of incident cardiovascular event according to body mass index categories

Characteristics	Total	Underweight	Normal weight	Overweight	Obese	
	n = 130 685	3816 (2.9%)	39 093 (29.9)	47 948 (36.7%)	39 823 (30.5)	*P*-value
Follow-up, median (IQR)	13.0 (8.2–17.0)	10.3 (5.6–15.1)	12.3 (7.6–16.5)	13.3 (8.6–17.2)	13.4 (8.8–17.4)	0.0001
Females	61 533 (47.1)	2770 (72.6)	20 150 (51.5)	19 443 (40.6)	19 170 (48.1)	<0.001
Age (years), median (IQR)	71 (61–79)	78 (68–86)	75 (65–83)	71 (62–79)	66 (57–75)	0.0001
Metabolic health status						<0.001
Metabolically healthy	43 189 (33.1)	1927 (50.5)	15 903 (40.7)	15 577 (32.5)	9782 (24.6)	
1 metabolic abnormality, *n* (%)	55 168 (42.2)	1527 (40.0)	16 432 (42.0)	20 609 (43.0)	16 600 (41.7)	
2 metabolic abnormalities, *n* (%)	26 938 (20.6)	327 (8.6)	5876 (15.0)	9910 (20.7)	10 825 (27.2)	
3 metabolic abnormalities, *n* (%)	5390 (4.1)	35 (0.9)	882 (2.3)	1852 (3.9)	2621 (6.6)	
Ethnicity						<0.001
Asian	3248 (2.5)	70 (1.8)	1029 (2.6)	1300 (2.7)	849 (2.1)	
Black	1188 (0.9)	20 (0.5)	263 (0.7)	418 (0.9)	487 (1.2)	
Mixed	302 (0.2)	4 (0.1)	81 (0.2)	120 (0.3)	97 (0.2)	
Other	1020 (0.8)	17 (0.5)	296 (0.8)	383 (0.8)	324 (0.8)	
White	119 031 (91.1)	3504 (91.8)	35384 (90.5)	43 535 (90.8)	36 608 (91.9)	
Unknown	5896 (4.5)	201 (5.3)	2040 (5.2)	2192 (4.6)	1463 (3.7)	
Socioeconomic status						<0.001
1 (least deprived)	25 860 (19.8)	705 (18.5)	8310 (21.3)	10 168 (21.2)	6677 (16.8)	
2	27 737 (21.2)	742 (19.4)	8397 (21.5)	10 646 (22.2)	7952 (20.0)	
3	27 261 (20.9)	778 (20.4)	8126 (20.8)	10 026 (20.9)	8331 (20.9)	
4	25 856 (19.8)	803 (21.0)	7440 (19.0)	9208 (19.2)	8405 (21.1)	
5 (most deprived)	23 849 (18.3)	782 (20.5)	6787 (17.4)	7855 (16.4)	8425 (21.2)	
Unknown	122 (0.1)	6 (0.2)	33 (0.1)	45 (0.1)	38 (0.1)	
Current smokers	26 363 (20.2)	1261 (33.1)	8874 (22.7)	8790 (18.3)	7437 (18.7)	<0.001
Alcohol problem	3838 (2.9)	217 (5.7)	1321 (3.4)	1190 (2.5)	1110 (2.8)	<0.001
Alcoholic liver disease	490 (0.4)	28 (0.7)	160 (0.4)	148 (0.3)	154 (0.4)	<0.001
Atrial fibrillation	13 504 (10.3)	521 (13.7)	4610 (11.8)	4556 (9.5)	3817 (9.6)	<0.001
Cancer	20 249 (15.5)	736 (19.3)	7191 (18.4)	7320 (15.3)	5002 (12.6)	<0.001
Chronic kidney disease	17 618 (13.5)	501 (13.1)	5298 (13.6)	6177 (12.9)	5642 (14.2)	<0.001
COPD	12 062 (9.2)	835 (21.9)	4396 (11.2)	3728 (7.8)	3103 (7.8)	<0.001
Dementia	2900 (2.2)	299 (7.8)	1370 (3.5)	830 (1.7)	401 (1.0)	<0.001
Erectile dysfunction	11 633 (8.9)	97 (2.5)	2451 (6.3)	4814 (10.0)	4271 (10.7)	<0.001
Family history of hyperlipidaemia	287 (0.2)	5 (0.1)	72 (0.2)	116 (0.2)	94 (0.2)	0.159
Family history of CVD	34 805 (26.6)	718 (18.8)	9396 (24.0)	13 096 (27.3)	11 595 (29.1)	<0.001
Heart failure	7642 (5.9)	285 (7.5)	2435 (6.2)	2465 (5.1)	2457 (6.2)	<0.001
Severe mental illness	1701 (1.3)	72 (1.9)	506 (1.3)	543 (1.1)	580 (1.5)	<0.001
Transient ischaemic attack	10.859 (8.3)	406 (10.6)	3824 (9.8)	4008 (8.4)	2621 (6.6)	<0.001
Anti-arrhythmic	7025 (5.4)	244 (6.4)	2224 (5.7)	2457 (5.1)	2100 (5.3)	<0.001
Anti-coagulant	10 276 (7.9)	266 (7.0)	3142 (8.0)	3563 (7.4)	3305 (8.3)	<0.001
Anti-diabetic	27 523 (21.1)	260 (6.8)	5420 (13.9)	9657 (20.1)	12 186 (30.6)	<0.001
Anti-hypertensive	84 443 (64.6)	1889 (49.5)	22 734 (58.2)	31 028 (64.7)	28 792 (72.3)	<0.001
Anti-platelets	54 056 (41.4)	1388 (36.4)	15 692 (40.1)	20 169 (42.1)	16 807 (42.2)	<0.001
Statin						<0.001
Low intensity	7335 (5.6)	108 (2.8)	1975 (5.1)	2880 (6.01)	2373 (6.0)	
Moderate intensity	36 718 (28.1)	583 (15.3)	9035 (23.1)	13 874 (28.9)	13 226 (33.2)	
High intensity	10 597 (8.1)	115 (3.0)	2114 (5.4)	3928 (8.2)	4440 (11.2)	

Nutritional status for the body mass index categories (kg/m^2): underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9) and obese (≥30). Metabolic abnormalities included the main components of the metabolic syndrome: dyslipidaemia, diabetes mellitus and arterial hypertension.

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease IQR, interquartile range; n, frequency/numbers.

risk regardless of the number of metabolic risk factors, but the incremental metabolic factors were not associated with increased risk of stroke within the underweight BMI subgroup.

Peripheral vascular disease

A similar pattern as for stroke was observed for PVD regarding the impact of BMI on the outcome. (a) When compared with metabolically healthy patients with normal BMI, the risk

Table 2 Characteristics of the study cohort at the time of incident cardiovascular event according to the metabolic state

Characteristics	Metabolically healthy 43 189 (33.1)	1 metabolic abnormality 55 168 (42.2)	2 metabolic abnormalities 26 938 (20.6)	3 metabolic abnormalities 5390 (4.1)	*p*-value
Follow-up, median (IQR)	12.4 (7.5–16.5)	13.0 (8.4–17.0)	13.4 (8.8–17.4)	14.1 (9.4–18.1)	0.0001
Females	19 557 (45.3)	26 657 (48.3)	12 703 (47.2)	2616 (48.5)	<0.001
Age (years), median (IQR)	67 (57–77)	72 (63–80)	72 (64–79)	71 (63–78)	0.0001
Body mass index (BMI) (kg/m^2)					
BMI, mean (SD)	26.6 (5.6)	27.8 (5.7)	29.3 (6.1)	30.6 (6.4)	0.0001
Underweight (< 18.5 kg/m^2), *n* (%)	1927 (4.5)	1527 (2.8)	327 (1.2)	35 (0.7)	<0.001
Normal (18.5–24.9 kg/m^2), *n* (%)	15 903 (36.8)	16 432 (29.8)	5876 (21.8)	882 (16.4)	
Overweight (25.0–29.9 kg/m^2), *n* (%)	15 577 (36.1)	20 609 (37.4)	9910 (36.8)	1852 (34.4)	
Obese (≥30.0 kg/m^2), *n* (%)	9782 (22.7)	16 600 (30.1)	10 825 (40.2)	2621 (48.6)	
Ethnicity					<0.001
Asian	778 (1.8)	1192 (2.2)	999 (3.7)	279 (5.2)	
Black	230 (0.5)	486 (0.9)	380 (1.4)	92 (1.7)	
Mixed	105 (0.2)	117 (0.2)	61 (0.2)	19 (0.4)	
Other	324 (0.8)	381 (0.7)	248 (0.9)	67 (1.2)	
White	39 608 (91.7)	50 453 (91.5)	24 177 (89.8)	4793 (88.9)	
Unknown	2144 (5.0)	2539 (4.6)	1073 (4.0)	140 (2.6)	
Socioeconomic status					<0.001
1 (least deprived)	8533 (19.8)	11 127 (20.2)	5223 (19.4)	977 (18.1)	
2	9155 (21.2)	11 935 (21.6)	5573 (20.7)	1074 (19.9)	
3	8896 (20.6)	11 434 (20.7)	5761 (21.4)	1170 (21.7)	
4	8443 (19.6)	10 884 (19.7)	5410 (20.1)	1119 (20.8)	
5 (most deprived)	8122 (18.8)	9741 (17.7)	4945 (18.4)	1041 (19.3)	
Unknown	40 (0.1)	47 (0.1)	26 (0.1)	9 (0.2)	
Current smokers	10 893 (25.2)	10 206 (18.5)	4346 (16.1)	917 (17.0)	<0.001
Alcohol problem	1484 (3.4)	1428 (2.6)	754 (2.8)	172 (3.2)	<0.001
Alcoholic liver disease	145 (0.3)	186 (0.3)	121 (0.5)	38 (0.7)	<0.001
Atrial fibrillation	3530 (8.2)	6202 (11.2)	3208 (11.9)	564 (10.5)	<0.001
Cancer	6016 (13.9)	8920 (16.2)	4381 (16.3)	932 (17.3)	<0.001
Chronic kidney disease	2217 (5.1)	7921 (14.4)	6004 (22.3)	1476 (27.4)	<0.001
COPD	4645 (10.8)	4967 (9.0)	2071 (7.7)	379 (7.0)	<0.001
Dementia	914 (2.1)	1228 (2.2)	641 (2.4)	117 (2.2)	0.147
Erectile dysfunction	2568 (6.0)	4550 (8.3)	3563 (13.2)	952 (17.7)	<0.001
Family history of hyperlipidaemia	75 (0.2)	120 (0.2)	75 (0.3)	17 (0.3)	0.014
Family history of CVD	10 377 (24.0)	15 128 (27.4)	7719 (28.7)	1581 (29.3)	<0.001
Heart failure	285 (7.5)	2435 (6.2)	2465 (5.1)	2457 (6.2)	<0.001
Severe mental illness	695 (1.6)	656 (1.2)	291 (1.1)	59 (1.1)	<0.001
Transient ischaemic attack	2903 (6.7)	5012 (9.3)	2438 (9.1)	416 (7.7)	<0.001
Anti-arrhythmic	2316 (5.4)	3074 (5.6)	1376 (5.1)	259 (4.8)	0.010
Anti-coagulant	2943 (6.8)	4498 (8.2)	2360 (8.8)	475 (8.8)	<0.001
Anti-diabetic	363 (0.8)	8257 (15.0)	14 520 (53.9)	4383 (81.3)	<0.001
Anti-hypertensive	13 344 (30.9)	41 769 (75.7)	24 221 (89.9)	5109 (94.8)	<0.001
Anti-platelets	13 333 (30.9)	23 540 (42.7)	14 072 (52.2)	3111 (57.7)	<0.001
Statin					<0.001
Low intensity	1148 (2.7)	3035 (5.5)	2537 (9.4)	615 (11.4)	
Moderate intensity	6495 (15.0)	15 638 (28.4)	11 943 (44.3)	2642 (49.0)	
High intensity	1298 (3.0)	3726 (6.8)	4048 (15.0)	1525 (28.3)	

Metabolic abnormalities included the main components of the metabolic syndrome: dyslipidaemia, diabetes mellitus and arterial hypertension.
Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease IQR, interquartile range; n, frequency/numbers; SD, standard deviation.

of subsequent PVD was lower in patients who are overweight and metabolically healthy, HR 0.65 (95% CI 0.58–0.72) or obese and metabolically healthy, HR 0.57 (95% CI 0.49–0.65, Table S5, Figure 2). Comparing patients of different BMI categories with a similar number of metabolic risk factors, higher BMI was constantly not associated with increased risk. (b) In contrast to the findings on stroke, within each BMI category the increasing number of metabolic risk factors related to increased risk (Figure 2).

Cardiovascular mortality

(a) The risk of cardiovascular-related mortality was lower in patients who are overweight, HR 0.76 (95% CI 0.70–0.84) or obese, HR 0.85 (95% CI 0.76–0.96) when compared with

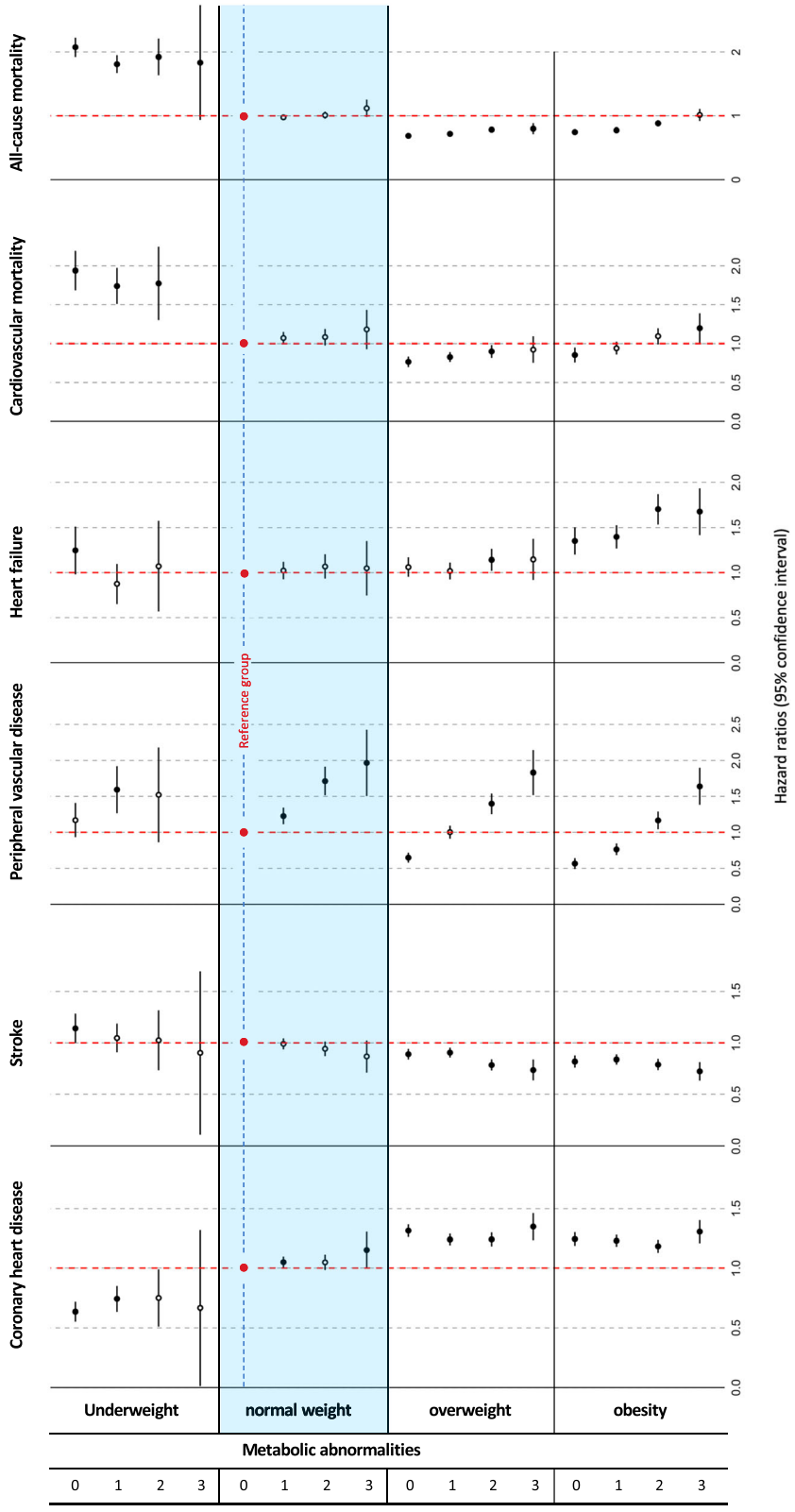

Figure 2 Association between body mass index and level of metabolic health with subsequent cardiovascular morbidity and mortality outcomes. Model adjusted for age at the time of incident cardiovascular disease event, sex, ethnicity, current smoker status, diagnosis of atrial fibrillation, cancer, chronic kidney disease, chronic obstructive pulmonary disease and heart failure.

patients with normal BMI (comparison for metabolically healthy patients) (Table S6). Also, for patients with 1 and 2 metabolic risk factors, overweight patients showed not higher but lower risk than normal BMI patients. (b) Within each BMI category a higher number of metabolic risk factors was associated with a trend for higher mortality risk (Figure 2).

All-cause mortality

(a) Similar to CV mortality, higher BMI was associated with lower all-cause mortality regardless of the level of metabolic health when compared with metabolically healthy patients who have normal BMI: patients with overweight: HR 0.69 (95% CI 0.65–0.72) or obesity, HR 0.75 (95% CI 0.70–0.79) (comparison for metabolically healthy patients). Also, for patients with increasing count of metabolic risk factors, overweight patients showed not higher but lower risk than normal BMI patients (Table S7, Figure 2). (b) Within each BMI category, patients with an increasing number of metabolic risk factors showed a trend for increased risk of all-cause mortality (Figure 2).

As a general trend in the entire patient cohort, a cumulative number of metabolic risk factors was associated with an increasing risk of subsequent CV morbidity and mortality outcome, except for stroke (Figure S1).

In turn, the association between BMI and individual cardiovascular morbidity and mortality outcomes for the entire patient cohort was non-linear as shown by the restricted cubic splines (Figure S2).

Discussions

The main finding from this study in a nationwide population-based cohort of 130 685 patients is that in long-term follow-up (median duration of 13.0 years) after the onset of cardiovascular disease the excessive BMI (overweight or obesity) was associated with a lower risk of subsequent stroke, peripheral vascular disease, and not with higher but with lower CV mortality and all-cause mortality. This inverse association of body weight and outcome was observed regardless of the level of additional metabolic risk factors. In turn, being underweight is constantly associated with increased mortality. Increasing numbers of classical metabolic risk factors other than overweight were associated with higher risk for all morbidity and mortality outcomes except for subsequent non-fatal stroke, where no such association was observed.

This analysis confirms several previous reports which showed that increasing BMI was associated with better outcomes in patients with existing cardiovascular disease.[4] The study extends current knowledge by showing that in patients with cardiovascular disease, this association of body weight and outcome is not influenced by the level of metabolic health, that is, the presence of classical metabolic risk factors including dyslipidaemia, diabetes mellitus or arterial hypertension.[14–16] Indeed, similar findings were reported in patients with diabetes mellitus[17] or pre-diabetes.[18]

These data add to the accumulating bulk of evidence that, in contrast to the firmly established understanding of obesity as a risk factor in primary prevention, in the presence of cardiovascular disease, excessive body weight by itself may not be regarded as an additional risk factor for impaired survival. In fact, a more differentiated perspective on body weight may be considered that distinguishes between primary prevention (i.e., healthy subjects) and secondary outcome prevention, where best—and longest—survival for patients with established cardiovascular disease has to be the treatment goal.

Despite the multiple and robust data that confirm this inverse relationship of body weight and outcome in a wide range of cardiovascular diseases in various study settings and applying different analysis methods, the discussion of potential underlying mechanisms is less well established and often dwells on potential methodical limitations, analytical bias or downright rejection of the observation. Common arguments include methodology pitfalls like reverse causation, lack of adjustment for residual confounders such as age, smoking, and unidentified co-morbidities, but also a limited precision of the BMI as a tool for body composition assessment. Reverse causation implies low body weight representing an index for the presence of chronic diseases like cancer, malnutrition, infectious disease, and smoking, which in turn may increase mortality.[19] Such factors may contribute to explaining the observed association, but this would not reject the association of higher body weight with better outcomes.

In our analysis, the results were adjusted for many prospectively registered patient characteristics like age, sex, ethnicity, smoking, socioeconomic status, multiple co-morbidities, and concurrent medication. We cannot exclude the possibility that additional unmeasured confounding factors might have been unequally distributed among BMI strata. However, key co-morbidities of cardiovascular risk are represented in the metabolic syndrome, comprising hypertension, diabetes, and hyperlipidaemia all being included in the multivariate-adjusted assessments. In fact, in our study in accordance with common knowledge, a higher, not lower, prevalence of such co-morbidities with higher body weight was observed. Therefore, a higher risk profile of relevant cardiovascular risk factors may be concluded for patients with higher BMI.

On the other hand, the reproducibility of these findings and mechanistic insights that suggest a benefit of excessive energy and protein reserves in the context of disease-related catabolic conditions may support a pathophysiologic concept of a favourable effect of higher body weight. Multiple signals involved in balancing metabolic regulation may contribute to an overall catabolic activation and anabolic blunting such as lower caloric intake, sedentary lifestyle, impaired intestinal

absorption, neuroendocrine activation, inflammatory activation, hormone imbalances and others.

The conclusions of this analysis cannot support the widely adopted recommendations for weight management towards weight reduction after a cardiovascular event, whereas the targeting of other cardiovascular risk factors is supported by the findings. Our observations are in line with and further illustrate the findings from the Look AHEAD (Action for Health in Diabetes) trial that tested the benefit of weight reduction in patients with type 2 diabetes, a disease that carries a high risk for cardiovascular events. In this prospective controlled treatment study, an intensive, multi-modular lifestyle intervention targeted towards weight reduction did not result in the hypothesized reduced cardiovascular event rates nor improved mortality despite the successful and sustained reduction in excessive body weight loss.[20] Further evidence is expected from ongoing randomized trials. Semaglutide, a glucagon-like peptide-1 analogue leads to sustained, clinically relevant reduction in body weight and is currently assessed for the reduction of cardiovascular risk in patients with overweight or obesity and established cardiovascular disease.[21,22]

Strengths and limitations

To our knowledge, our study is the largest study of individuals with incident CVD identified from a nationwide population to assess the association between BMI, metabolic health and clinical outcomes following incident cardiovascular event using multiple data linkages with a long follow-up period (median of 13.0 years), maximising the ascertainment of subsequent outcomes. This study has a number of strengths. First, the size and representativeness of the CPRD GOLD dataset – this large retrospective nationwide population-based study used primary care data which is representative of the UK population,[5] linked to hospitalisation and mortality records. We, therefore, assume the estimated risk of subsequent cardiovascular morbidity and mortality outcomes accurately reflects the risk in the wider UK population. Additionally, multiple covariates including socioeconomic status were accounted for in the analyses. We acknowledge limitations generally inherent in studies using electronic health records (EHRs). Potential ascertainment and information bias are acknowledged. The coded definitions of outcomes and CVD incident diagnosis used in this study are, however, well-established due to the pay-for-performance scheme (Quality and Outcome Framework) which has improved documentation/coding for cardiovascular conditions and associated risk factors.[23] The potential for misclassification bias is likely not high.

Conclusions

In patients with incident CVD, overweight and obesity were related to a more favourable prognosis for subsequent stroke, PVD, and mortality (CVD-related and all-cause) irrespective of the level of metabolic health, that is, the presence of additional metabolic risk factors. Increasing number of metabolic risk factors (i.e., diabetes, dyslipidaemia and hypertension) increased the risk of cardiovascular morbidity and mortality outcomes in patients with incident cardiovascular disease, but this was not observed for increased body weight alone.

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Conflict of interest

W. Doehner reports consulting fees and speaker honoraria from Aimediq, Bayer, Boehringer Ingelheim, Boston Scientific, Cardiomatics, Lilly, Medtronic, Vifor Pharma, travel support from Pharmacosmos, and research support to the Institute from EU (Horizon2020), German Ministry of Education and Research, German Center for Cardiovascular Research, Boehringer Ingelheim, Vifor Pharma. RKA and GN report no conflict of interest.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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