ORIGINAL ARTICLE

Journal of Cachexia, Sarcopenia and Muscle 2021; **12**: 2111–2121
Published online 27 September 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12818

Obesity and long-term outcomes after incident stroke: a prospective population-based cohort study

Ralph K. Akyea[1]*, Wolfram Doehner[2,3,4], Barbara Iyen[1], Stephen F. Weng[1], Nadeem Qureshi[1] & George Ntaios[5]

[1]*Primary Care Stratified Medicine, School of Medicine, University of Nottingham, Nottingham, UK;* [2]*Berlin Institute of Health, Charité—Universitätsmedizin Berlin, BIH Center for Regenerative Therapies (BCRT), Berlin, Germany;* [3]*Department of Internal Medicine and Cardiology (Virchow Klinikum), Charité Universitätsmedizin Berlin, and German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany;* [4]*Center for Stroke Research Berlin (CSB), Charité Universitätsmedizin Berlin, Berlin, Germany;* [5]*Department of Internal Medicine, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece*

Abstract

Background The association between obesity, major adverse cardiovascular events (MACE), and mortality in patients with incident stroke is not well established. We assessed the relationship between body mass index (BMI) and MACE in patients with incident stroke.

Methods The population-based cohort study identified 30 702 individuals from the Clinical Practice Research Datalink (CPRD GOLD) and Hospital Episode Statistics (HES) databases from the United Kingdom. Individuals were aged ≥18 years with incident stroke between 1-1-1998 and 31-12-2017, a BMI recorded within 24 months before incident stroke, and no prior history of MACE. BMI was categorized as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obesity class I (30.0–34.9 kg/m^2), class II (35.0–39.9 kg/m^2) and class III (≥40 kg/m2). MACE was defined as a composite of incident coronary heart disease, recurrent stroke, peripheral vascular disease (PVD), heart failure, and cardiovascular-related mortality. Multivariable Cox regression was used to assess differences in MACE risk between BMI categories.

Results At baseline, 1217 (4.0%) were underweight, 10 783 (35.1%) had a normal BMI, 10 979 (35.8%) had overweight, 5206 (17.0%) had obesity Class I, 1749 (5.7%) Class II, and 768 (2.5%) Class III. In multivariable analysis, higher BMI were associated with lower risk of *subsequent MACE* [overweight: HR 0.96, 95% CI 0.93–0.99)]; *PVD* [overweight: 0.65 (0.49–0.85); obesity Class III: 0.19 (0.50–0.77)]; *cardiovascular-related death* [overweight: 0.80 (0.74–0.86); obesity Class I: 0.79 (0.71–0.88); Class II: 0.80 (0.67–0.96)]; and *all-cause mortality* [overweight: 0.75 (0.71–0.79); obesity Class I: 0.75 (0.70–0.81); Class II: 0.77 (0.68–0.86)] when compared to those with normal BMI. The results were similar irrespective of sex, diabetes mellitus, smoking or cancer at time of incident stroke.

Conclusions In patients with incident stroke, overweight or obesity were associated with a more favourable prognosis for subsequent MACE, PVD, and mortality, irrespective of sex, diabetes mellitus, smoking, or cancer at baseline. As with other cohort studies, our study demonstrates an association. Randomized control trials should be considered to robustly evaluate the impact of weight management recommendations on subsequent cardiovascular outcomes in stroke survivors.

Keywords stroke–obesity paradox; stroke; body mass index; electronic health records; real-world evidence

Received: 4 July 2021; Revised: 16 August 2021; Accepted: 5 September 2021
**Correspondence to: Dr Ralph Kwame Akyea, Primary Care Stratified Medicine, School of Medicine, University of Nottingham, University Park Campus, Nottingham NG7 2RD, UK. Phone: +44 (0)115 748 6834. Email: ralph.akyea1@nottingham.ac.uk*

Introduction

Obesity is an established risk factor for stroke,[1] but the association of increased body mass index (BMI) with survival after stroke remains contentious. Contrary to evidence in the general population,[2] in patients with established cardiovascular disease, increased BMI has been shown to be independently associated with better outcome.[3–6] Many studies have shown that increased BMI has a protective effect on survival after stroke,[7,8] while other studies have not confirmed an obesity paradox in patients with stroke.[9] The association between BMI and composite major adverse cardiovascular event (MACE) and its individual constituent outcomes have, however, not been studied using a population-based cohort in patients with any subtype of incident stroke.

Using a large population-based cohort in the United Kingdom, this study aimed to examine the relationship between BMI and MACE outcomes during long-term follow-up in patients with any subtype of incident stroke.

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,[10] linked to secondary care hospitalization data [Hospital Episode Statistics (HES)],[11] national mortality data [Office for National Statistics (ONS)],[12] and social deprivation data [Index of Multiple Deprivation (IMD) 2015].[13] Individuals included in CPRD GOLD database, from a network of general practices across the UK, are representative of the UK general population in terms of sex, age, and ethnicity,[10] thereby validating CPRD GOLD for epidemiological research. This study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (Protocol number 19_023R). Requests to access CPRD data are made through the Independent Scientific Advisory Committee (www.cprd.com).

Study population

We identified a cohort of individuals with incident non-fatal stroke in either primary care (CPRD GOLD) or secondary care (HES) between 1 January 1998 and 31 December 2017. Details about this cohort were previously reported.[14] Individuals with a record of major adverse cardiovascular event [including coronary heart disease (CHD), peripheral vascular disease (PVD), or heart failure] before incident stroke were excluded. Individuals were followed from date of incident stroke diagnosis until they developed a major adverse outcome, died, ceased contributing data, or end of data collection. The study flow diagram is shown in Supporting information, *Figure S1*.

Cohort demographics and baseline characteristics

Age was defined at the time of incident stroke. Ethnicity was categorized into six groups: Asian, Black, Mixed, Other, White, and unknown.[15] To describe socioeconomic status, the English Index of Multiple Deprivation 2015[13] linked to the individual's residential postcode was used. IMD is a weighted mean across the seven domains, hence offers a single score to describe the concept of deprivation; categorized into quintiles [Quintile 1 (least deprived group) to Quintile 5 (most deprived group)]. Medication prescriptions (issue of prescription) at baseline were defined as a prescription within 12 months before incident stroke. For cholesterol (low-density lipoprotein, high-density lipoprotein, and total), BMI, blood pressure measures (diastolic and systolic), and glomerular filtration rate (GFR), the most recent values/measures within 24 months before incident stroke were used. All other comorbidities were defined based on the latest record before incident stroke.

Body mass index

BMI 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), obesity Class I (BMI 30.0–34.9 kg/m^2), obesity Class II (BMI 35.0–39.9 kg/m^2), obesity Class III (BMI $\geq$ 40 kg/m^2).[16] Accordingly, and in line with accumulating epidemiologic evidence, we used as reference group (normal weight) patients with a BMI of 18.5–24.9 kg/m^2.[17]

Outcome measures

First subsequent MACE after incident stroke was the primary outcome. MACE was defined as a composite of new onset coronary heart disease, recurrent stroke, PVD, heart failure, or cardiovascular-related mortality, based on record from across the linked data sources (CPRD, HES, or ONS registry). All-cause mortality was considered as a secondary outcome.

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 online (www.caliberresearch.org/portal/).[18]

Table 1 Characteristics of study population at time of incident stroke according to body mass index categories

Characteristics	<18.5 *n* (%) 1217 (4.0%)	18.5–24.9 *n* (%) 10 783 (35.1%)	25.0–29.9 *n* (%) 10 979 (35.8%)	30.0–34.9 *n* (%) 5206 (17.0%)	35.0–39.9 *n* (%) 1749 (5.7%)	≥ 40 kg/m^2 *n* (%) 768 (2.5%)	*P* value
Follow-up, median (IQR)	10.2 (5.7–15.4)	12.1 (7.2–16.6)	13.4 (8.5–17.5)	13.8 (8.8–17.8)	13.3 (8.7–17.5)	13.8 (8.2–17.7)	0.0001
Females	935 (76.8)	6144 (57.0)	5164 (47.0)	2620 (50.3)	1025 (58.6)	511 (66.5)	<0.001
Age (years) median (IQR)	81 (72–87)	78 (69–85)	74 (65–81)	71 (62–79)	68 (58–75)	63.5 (53–72)	0.0001
Incident stroke subtype							<0.001
Haemorrhagic stroke	146 (12.0)	1037 (9.6)	869 (7.9)	383 (7.4)	139 (8.0)	54 (7.0)	
Ischaemic stroke	437 (35.9)	3996 (37.1)	4204 (38.3)	2071 (39.8)	703 (40.2)	323 (42.1)	
Stroke (not specified)	634 (52.1)	5750 (53.3)	5906 (53.8)	2752 (52.9)	907 (51.9)	391 (50.9)	
Ethnicity							<0.001
Asian	18 (1.5)	191 (1.8)	197 (1.8)	84 (1.6)	23 (1.3)	4 (0.7)	
Black	9 (0.7)	89 (0.8)	105 (1.0)	86 (1.7)	39 (2.2)	20 (2.6)	
Mixed	0	12 (0.1)	13 (0.1)	11 (0.2)	3 (0.2)	3 (0.4)	
Other	6 (0.5)	75 (0.7)	80 (0.7)	38 (0.7)	13 (0.7)	4 (0.5)	
White	1116 (91.7)	9758 (90.5)	10 031 (91.4)	4748 (91.2)	1598 (91.4)	704 (91.7)	
Unknown	68 (5.6)	658 (6.1)	553 (5.0)	239 (4.6)	73 (4.2)	32 (4.2)	
Socioeconomic status							<0.001
1 (least deprived)	233 (19.2)	2369 (22.0)	2386 (21.7)	926 (17.8)	249 (14.2)	94 (12.2)	
2	257 (21.1)	2368 (22.0)	2443 (22.3)	1124 (21.6)	368 (21.0)	143 (18.6)	
3	243 (20.0)	2288 (21.2)	2275 (20.7)	1077 (20.7)	372 (21.3)	177 (23.1)	
4	272 (22.4)	1987 (18.4)	2124 (19.4)	1062 (20.4)	374 (21.4)	165 (21.5)	
5 (most deprived)	210 (17.3)	1763 (16.4)	1737 (15.8)	1012 (19.4)	384 (22.0)	189 (24.6)	
Unknown	2 (0.2)	8 (0.1)	14 (0.1)	5 (0.1)	2 (0.1)	0	
Current smokers	349 (28.7)	2177 (20.2)	1841 (16.8)	874 (16.8)	306 (17.5)	142 (18.5)	<0.001
DBP (mmHg)	78 (70–82)	79 (70–83)	80 (71–85)	80 (73–86)	80 (74–86)	80 (75–88)	<0.001
SBP (mmHg)	138 (122–149)	139 (128–148)	140 (130–150)	140 (130–150)	140 (130–150)	140 (130–150)	<0.001
HDL cholesterol (mmol/L)	1.8 (1.5–2.0)	1.6 (1.3–1.8)	1.4 (1.2–1.6)	1.3 (1.1–1.5)	1.2 (1.1–1.4)	1.1 (1.0–1.3)	0.0001
LDL cholesterol (mmol/L)	2.8 (2.5–3.2)	2.9 (2.5–3.3)	2.9 (2.4–3.4)	2.9 (2.3–3.4)	2.9 (2.3–3.4)	2.9 (2.4–3.5)	0.0001
Total cholesterol (mmol/L)	5.2 (4.6–5.6)	5.1 (4.5–5.5)	5.0 (4.4–5.6)	5.0 (4.3–5.6)	5.0 (4.3–5.6)	5.0 (4.4–5.5)	0.0001
GFR	67.5 (60.3–74.7)	67.0 (60.3–73.0)	67.4 (60.9–73.1)	68.0 (61.0–73.9)	68.7 (61.6–75.3)	69.2 (63.0–76.0)	0.0001
Comorbidities at baseline							
Alcohol problem	61 (5.0)	366 (3.4)	300 (2.7)	164 (3.2)	48 (2.7)	28 (3.7)	<0.001
Atrial fibrillation	154 (12.7)	1273 (11.8)	1159 (10.6)	483 (9.3)	166 (9.5)	74 (9.6)	<0.001
Cancer	256 (21.0)	2273 (21.1)	1956 (17.8)	818 (15.7)	227 (13.0)	97 (12.6)	<0.001
Chronic kidney disease	163 (13.4)	1491 (13.8)	1601 (14.6)	824 (15.8)	281 (16.1)	102 (13.3)	0.005
Diabetes mellitus	121 (9.9)	1672 (15.5)	2515 (22.9)	1589 (30.5)	660 (37.7)	295 (38.4)	<0.001
Type-1 diabetes	11 (0.9)	142 (1.3)	174 (1.6)	105 (2.0)	40 (1.3)	23 (3.0)	<0.001
Type-2 diabetes	95 (7.8)	1331 (12.3)	2112 (19.2)	1408 (27.1)	594 (34.0)	265 (34.5)	<0.001
Dyslipidaemia	76 (6.2)	1215 (11.3)	1569 (14.3)	846 (16.3)	291 (16.6)	124 (16.2)	<0.001
Hypertension	528 (43.4)	5555 (51.5)	6402 (58.3)	3359 (64.5)	1164 (66.6)	503 (65.5)	<0.001
Transient ischaemic attack	263 (21.6)	2472 (22.9)	2629 (24.0)	1167 (22.4)	336 (19.2)	131 (17.1)	<0.001
Prescribed medications at baseline							

(*Continues*)

Table 1 (continued)

Characteristics	<18.5 *n* (%) 1217 (4.0%)	18.5–24.9 *n* (%) 10 783 (35.1%)	25.0–29.9 *n* (%) 10 979 (35.8%)	30.0–34.9 *n* (%) 5206 (17.0%)	35.0–39.9 *n* (%) 1749 (5.7%)	≥ 40 kg/m^2 *n* (%) 768 (2.5%)	*P* value
ACE inhibitor	287 (23.6)	3518 (32.6)	4455 (40.6)	2637 (50.7)	958 (54.8)	429 (55.9)	<0.001
Anti-diabetic	73 (6.0)	1272 (11.8)	2025 (18.4)	1326 (25.5)	556 (31.8)	254 (33.1)	<0.001
Anti-hypertensive	550 (45.2)	5732 (53.2)	6759 (61.6)	3587 (68.9)	1260 (72.0)	545 (71.0)	<0.001
Antiplatelets	495 (40.7)	4605 (42.7)	4806 (43.8)	2286 (43.9)	745 (42.6)	310 (40.4)	0.090
Beta-blockers	265 (21.8)	2604 (24.2)	2996 (27.3)	1480 (28.4)	560 (32.0)	246 (32.0)	<0.001
Calcium channel blocker	280 (23.0)	2873 (26.6)	3469 (31.6)	1789 (34.4)	657 (37.6)	264 (34.4)	<0.001
NSAIDS	234 (19.2)	2508 (23.3)	3030 (27.6)	1675 (32.2)	598 (34.2)	284 (37.0)	<0.001
Statin							<0.001
Low intensity	39 (3.2)	477 (4.4)	596 (5.4)	281 (5.4)	107 (6.1)	36 (4.7)	
Moderate intensity	210 (17.3)	2370 (22.0)	3115 (28.4)	1627 (31.3)	567 (32.4)	240 (31.3)	
High intensity	32 (2.6)	524 (4.9)	755 (6.9)	488 (9.4)	188 (10.8)	87 (11.3)	

ACE, angiotensin converting enzyme; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; *n*, frequency/numbers; NSAIDS, non-steroidal anti-inflammatory drug; SBP, systolic blood pressure; %, percentage.
Nutritional status for the body mass index categories (kg/m^2): underweight (<18.5); normal weight (18.5–24.9); pre-obese (25.0–29.9); obesity Class I (30.0–34.9); obesity Class II (35.0–39.9); obesity Class III (≥40).

Statistical analysis

The Shapiro–Wilk test was used to assess normality of distribution for continuous variables.[19] Kruskal–Wallis test for continuous data and χ^2 test for categorical data were used to compare baseline characteristics between BMI categories. The level of missing values ranged between 3.1% for blood pressure measures to 57.4% for GFR. Details on the proportion of missingness is provided in *Table S1*. To estimate missing values for BMI, systolic and diastolic blood pressures, GFR, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol levels, multiple imputation by chained equations was used to generate 10 imputed datasets using all the other available patient variables.[20] The imputed datasets were pooled into a single dataset using Rubin's rules.[21] Differences in baseline characteristics between those with and without a BMI record within 24 months of incident stroke is provided in the *Table S2*. Event rates between BMI categories were analysed by multivariable Cox regression models using the category of normal BMI as reference. Time to event curves for BMI categories were made for MACE outcomes. Hazard ratios (HRs) and 95% confidence intervals (95% CI) for the outcomes according to BMI category were calculated in Cox regression models adjusted for: (a) age and sex; (b) age, sex, socioeconomic status, current smoking, history of alcohol problem, atrial fibrillation, chronic kidney disease, diabetes mellitus, dyslipidaemia, hypertension, transient ischaemic attack, prescription of angiotensin-converting enzyme (ACE) inhibitor, anti-hypertensive, anti-diabetic, anti-platelet, beta-blocker, calcium channel blocker, non-steroidal anti-inflammatory drugs, statin potency, diastolic and systolic blood pressure, GFR, total cholesterol (full adjustment model). Restricted cubic spline with 3–5 knots (lowest Akaike information criterion) was used for non-linear relationship between BMI and outcomes. All statistical analyses were performed using Stata SE version 16.1 (StataCorp LP). An alpha level of 0.05 was used for all analysis to define statistical significance.

Results

A total of 30 702 individuals with baseline BMI record (53% women) were included in this study. The median age for the study cohort was 75 years (IQR: 65–82). The distribution of BMI within the study cohort is present in *Figure S2*. Most of the individuals were within the overweight and obesity categories (60.9%) and 35.1% had normal BMI. Clinical characteristics and medications prescribed at baseline across the BMI categories are presented in Table 1 and by sex in *Table S3*. Individuals in the obese classes (I–III) were younger

Table 2 Number and proportion of first subsequent outcomes within the body mass index categories

Outcomes	<18.5 *n* = 1217 (4.0%)	18.5–24.9 *n* = 10 783 (35.1%)	25.0–29.9 *n* = 10 979 (35.8%)	30.0–34.9 *n* = 5206 (17.0%)	35.0–39.9 *n* = 1749 (5.7%)	≥40 kg/m^2 *n* = 768 (2.5%)	*P* value
Composite MACE							
Follow-up time	0.14 (0.03–1.10)	0.21 (0.03–1.46)	0.27 (0.04–1.77)	0.23 (0.03–1.66)	0.19 (0.03–1.67)	0.16 (0.03–1.28)	0.0001
Number of events (percent)	806 (66.2)	7326 (67.9)	7497 (68.3)	3545 (68.1)	1217 (69.6)	490 (63.8)	0.064
CHD							
Follow-up time	0.83 (0.28–2.20)	1.49 (0.31–3.42)	1.91 (0.60–4.59)	1.76 (0.52–3.86)	2.89 (1.03–4.62)	1.62 (0.90–3.79)	0.0001
Number of events (percent)	24 (2.0)	378 (3.5)	459 (4.2)	252 (4.8)	86 (4.9)	27 (3.5)	<0.001
Recurrent stroke							
Follow-up time	0.15 (0.04–1.03)	0.18 (0.03–1.24)	0.19 (0.03–1.29)	0.15 (0.02–1.15)	0.11 (0.03–1.02)	0.10 (0.02–1.05)	0.0001
Number of events (percent)	490 (40.3)	5119 (47.5)	5580 (50.8)	2636 (50.6)	908 (51.9)	379 (49.4)	<0.001
PVD							
Follow-up time	1.83 (1.07–2.76)	1.22 (0.50–2.89)	1.58 (0.77–4.63)	2.13 (0.73–4.67)	2.26 (1.22–3.74)	4.93 (1.23–8.63)	0.2636
Number of events (percent)	17 (1.4)	114 (1.1)	97 (0.9)	61 (1.2)	19 (1.1)	2 (0.3)	0.087
Heart failure							
Follow-up time	1.56 (0.64–3.35)	1.23 (0.32–3.47)	2.33 (0.74–4.64)	2.12 (0.54–5.62)	2.14 (0.59–4.70)	2.68 (1.30–5.84)	0.004
Number of events (percent)	20 (1.6)	209 (1.9)	241 (2.2)	136 (2.6)	62 (3.5)	20 (2.6)	<0.001
Cardiovascular mortality							
Follow-up time	0.07 (0.02–0.83)	0.09 (0.02–1.37)	0.10 (0.02–1.95)	0.12 (0.02–2.15)	0.16 (0.02–2.64)	0.09 (0.01–0.90)	0.0797
Number of events (percent)	255 (21.0)	1506 (14.0)	1120 (10.2)	460 (8.8)	142 (8.1)	62 (8.1)	<0.001
All-cause mortality							
Follow-up time	0.35 (0.4–2.29)	0.68 (0.06–3.25)	0.84 (0.06–4.17)	1.05 (0.06–4.14)	0.69 (0.06–4.18)	0.43 (0.04–2.38)	0.0001
Number of events (percent)	573 (47.1)	3421 (31.7)	2557 (23.3)	1053 (20.2)	314 (18.0)	140 (18.2)	<0.001

CHD, coronary heart disease; MACE, major adverse cardiovascular event; PVD, peripheral vascular disease.
Follow-up time: Time from incident stroke event to first subsequent event reported as median with interquartile range in years

Table 3 Outcomes in body mass index subgroups

Outcomes	<18.5 *n* = 1217 (4.0%) HR (95% CI)	25.0–29.9 *n* = 10 979 (35.8%) HR (95% CI)	30.0–34.9 *n* = 5206 (17.0%) HR (95% CI)	35.0–39.9 i = 1749 (5.7%) HR (95% CI)	≥ 40 kg/m^2 *n* = 768 (2.5%) HR (95% CI)
Composite MACE					
Age and sex adjusted	1.14 (1.06–1.23)	0.96 (0.93–0.99)	0.98 (0.95–1.03)	1.10 (1.04–1.17)	1.07 (0.97–1.17)
Full adjustment	1.12 (1.05–1.21)	0.96 (0.93–0.99)	0.98 (0.94–1.02)	1.08 (1.01–1.15)	1.04 (0.95–1.14)
CHD					
Age and sex adjusted	0.81 (0.53–1.22)	1.00 (0.87–1.15)	1.20 (1.02–1.41)	1.29 (1.01–1.63)	1.01 (0.68–1.51)
Full adjustment	0.85 (0.56–1.29)	0.94 (0.82–1.09)	1.05 (0.89–1.24)	1.06 (0.83–1.35)	0.82 (0.55–1.23)
Recurrent stroke					
Age and sex adjusted	1.01 (0.92–1.10)	1.00 (0.97–1.04)	1.00 (0.96–1.05)	1.07 (1.00–1.15)	1.05 (0.94–1.16)
Full adjustment	1.00 (0.91–1.09)	1.01 (0.98–1.05)	1.02 (0.97–1.07)	1.09 (1.02–1.18)	1.06 (0.95–1.18)
PVD					
Age and sex adjusted	1.96 (1.17–3.26)	0.71 (0.54–0.93)	1.00 (0.73–1.37)	1.02 (0.62–1.66)	0.28 (0.07–1.14)
Full adjustment	1.91 (1.14–3.19)	0.65 (0.49–0.85)	0.79 (0.57–1.09)	0.70 (0.42–1.17)	0.19 (0.05–0.77)
Heart failure					
Age and sex adjusted	1.09 (0.69–1.74)	1.12 (0.93–1.35)	1.60 (1.28–1.99)	2.62 (1.96–3.50)	2.60 (1.63–4.15)
Full adjustment	1.13 (0.71–1.80)	1.05 (0.87–1.26)	1.41 (1.12–1.76)	2.10 (1.56–2.83)	1.97 (1.23–3.17)
Cardiovascular mortality					
Age and sex adjusted	1.57 (1.38–1.80)	0.80 (0.74–0.87)	0.82 (0.74–0.91)	0.89 (0.75–1.06)	1.16 (0.90–1.50)
Full adjustment	1.53 (1.34–1.75)	0.80 (0.74–0.86)	0.79 (0.71–0.88)	0.80 (0.67–0.96)	1.02 (0.79–1.32)
All-cause mortality					
Age and sex adjusted	1.73 (1.58–1.89)	0.75 (0.71–0.79)	0.76 (0.70–0.81)	0.80 (0.71–0.90)	1.06 (0.89–1.26)
Full adjustment	1.64 (1.50–1.80)	0.75 (0.71–0.79)	0.75 (0.70–0.81)	0.77 (0.68–0.86)	0.99 (0.84–1.18)

CHD, coronary heart disease; HR, hazards ratio; MACE, major adverse cardiovascular event; PVD, peripheral vascular disease.
Full adjustment for age, sex, socioeconomic status, current smoking, history of alcohol problem, atrial fibrillation, chronic kidney disease, diabetes mellitus, dyslipidaemia, hypertension, transient ischaemic attack, prescription of ACE inhibitor, anti-hypertensive, anti-diabetic, anti-platelet, beta-blocker, calcium channel blocker, non-steroidal anti-inflammatory drug, statin potency, diastolic and systolic blood pressure, glomerular filtration rate, total cholesterol.
Reference category: Normal weight patients with a BMI of 18.5–24.9 kg/m^2

Table 4 Outcomes in body mass index subgroups excluding patients with cancer at time of incident stroke (*n* = 25 075)

Outcomes	<18.5 *n* = 961 (3.8%) HR (95% CI)	25.0–29.9 *n* = 9023 (36.0%) HR (95% CI)	30.0–34.9 *n* = 4388 (17.5%) HR (95% CI)	35.0–39.9 *n* = 1522 (6.1%) HR (95% CI)	≥40 kg/m^2 *n* = 671 (2.7%) HR (95% CI)
Composite MACE					
Full adjustment	1.13 (1.04–1.22)	0.97 (0.93–1.00)	0.97 (0.93–1.02)	1.07 (1.00–1.15)	1.06 (0.96–1.17)
CHD					
Full adjustment	0.99 (0.65–1.52)	0.95 (0.82–1.11)	1.05 (0.87–1.25)	1.06 (0.82–1.37)	0.84 (0.55–1.27)
Recurrent stroke					
Full adjustment	1.00 (0.90–1.11)	1.02 (0.98–1.07)	1.02 (0.97–1.08)	1.10 (0.12–1.19)	1.08 (0.97–1.21)
PVD					
Full adjustment	1.92 (1.09–3.40)	0.69 (0.51–0.92)	0.73 (0.51–1.05)	0.72 (0.43–1.22)	0.21 (0.05–0.85)
Heart failure					
Full adjustment	0.89 (0.49–1.60)	1.05 (0.85–1.30)	1.46 (1.14–1.87)	2.12 (1.53–2.94)	2.11 (1.27–3.50)
Cardiovascular mortality					
Full adjustment	1.48 (1.27–1.72)	0.78 (0.71–0.85)	0.77 (0.68–0.86)	0.77 (0.64–0.94)	1.10 (0.84–1.45)
All-cause mortality					
Full adjustment	1.68 (1.52–1.86)	0.74 (0.70–0.79)	0.73 (0.67–0.80)	0.75 (0.66–0.86)	1.03 (0.85–1.25)

CHD, coronary heart disease; HR, hazards ratio; MACE, major adverse cardiovascular event; PVD, peripheral vascular disease.
Full adjustment for age, sex, socioeconomic status, current smoking, history of alcohol problem, atrial fibrillation, chronic kidney disease, diabetes mellitus, dyslipidaemia, hypertension, transient ischaemic attack, prescription of ACE inhibitor, anti-hypertensive, anti-diabetic, anti-platelet, beta-blocker, calcium channel blocker, non-steroidal anti-inflammatory drug, statin potency, diastolic and systolic blood pressure, glomerular filtration rate, total cholesterol.
Reference category: Normal weight patients with a BMI of 18.5–24.9 kg/m^2

and had higher prevalence of hypertension and diabetes mellitus at baseline.

During a median follow-up of 12.9 years (IQR: 7.9–17.2 years), 20 881 (68.0%) individuals had a subsequent MACE recorded. The proportion of subsequent MACE outcomes was similar across the BMI categories. *Table 2* details the number and proportion for all the MACE and all the individual constituent outcomes.

In multivariable analysis, higher BMI were associated with lower risk of subsequent MACE [overweight: HR 0.96 (95% CI 0.93–0.99)]; PVD [overweight: HR 0.65 (95% CI 0.49–0.85); obesity Class III: HR 0.19 (95% CI 0.50–0.77)]; cardiovascular-related death [overweight: HR 0.80 (95% 0.74–0.86); obesity Class I: HR 0.79 (95% CI 0.71–0.88); obesity Class II: HR 0.80 (95% CI 0.67–0.96)]; and all-cause mortality [overweight: HR 0.75 (95% CI 0.71–0.79); obesity Class I: HR 0.75 (95% CI 0.70–0.81); obesity Class II: HR 0.77 (95% CI 0.68–0.86)] when compared with those with normal BMI—*Table 3*. *Tables* S4, S5, and S6 present the results disaggregated by sex, diabetes mellitus, and smoking status at time of incident stroke, respectively. *Tables 4* and S7 presents similar results after excluding 5627 (18.3%) individuals with a cancer diagnosis at baseline and excluding 8735 (28.5%) individuals with first subsequent outcomes within 30 days of incident stroke, respectively. The Kaplan–Meier curves for MACE and all-cause mortality across the BMI categories over a 10-year follow-up period is presented in *Figure 1*.

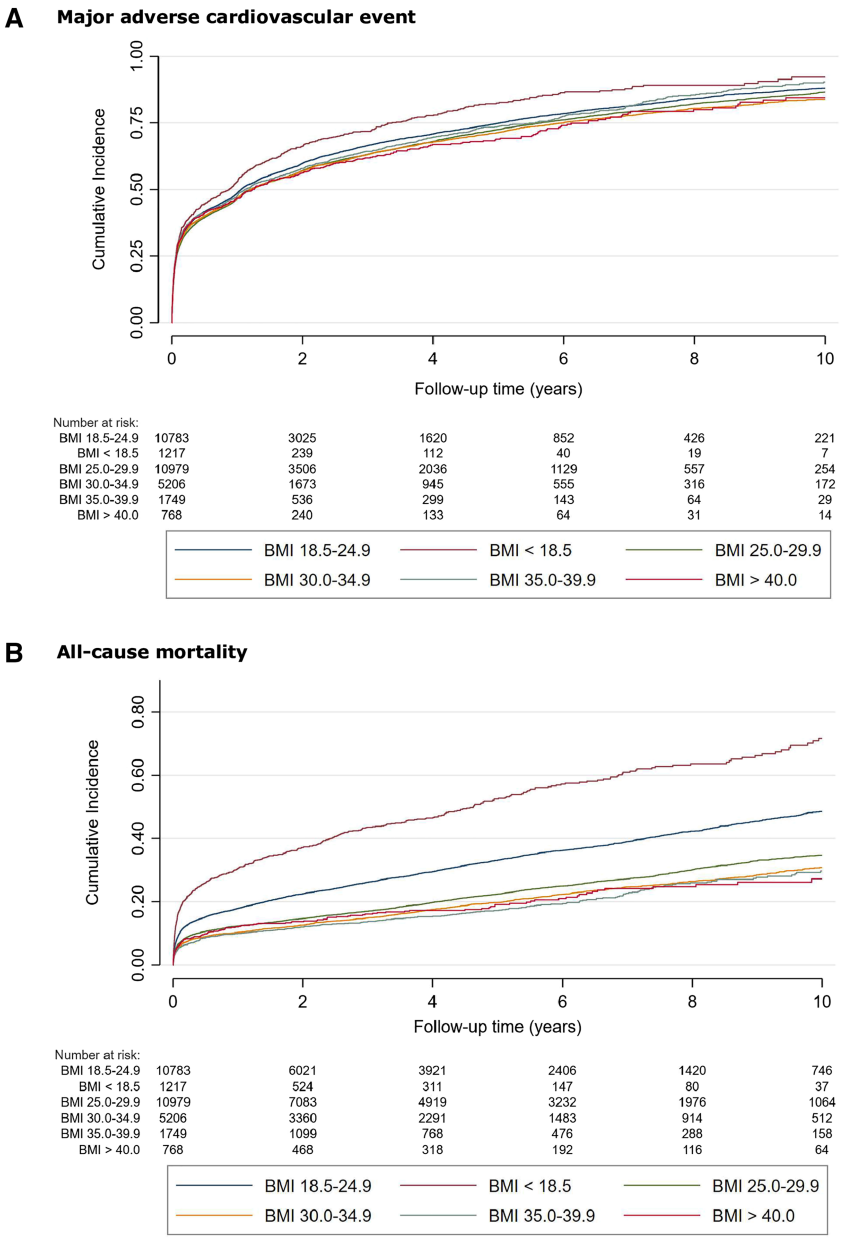

Figure 1 (*A,B*) Kaplan–Meier plots. BMI, body mass index.

DOI: 10.1002/jcsm.12818

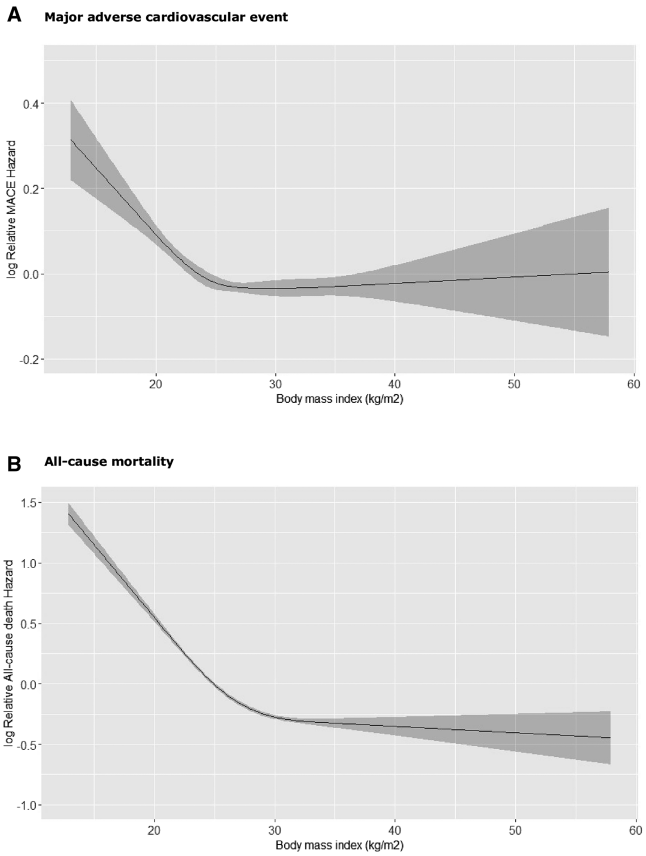

Figure 2 (*A,B*) Restricted cubic splines for the association between body mass index (continuous variable) and outcomes. MACE, major adverse cardiovascular event.

When compared with normal BMI, underweight was associated with a higher risk of MACE [HR 1.12 (95% CI 1.05–1.21)], PVD [HR 1.91 (95% CI 1.14–3.19)], cardiovascular-related death [HR 1.53 (95% CI 1.34–1.75)], and all-cause mortality [HR 1.64 (95% CI 1.50–1.80)].

Individuals who were obese had a higher risk of subsequent heart failure [obesity Class I: HR 1.41 (95% CI 1.12–1.76); obesity Class II: HR 2.10 (95% CI 1.56–2.83); obesity class III: HR 1.97 (95% CI 1.23–3.17)] when compared with those with a normal BMI.

The association between BMI and MACE as well as all-cause mortality was non-linear as shown by the restricted cubic splines, *Figure 2*. The risk for both subsequent MACE and all-cause mortality outcomes were significantly higher at lower BMI and lower from BMI greater than 25 kg/m^2.

Discussion

In this prospective population-base cohort study of 30 702 patients with incident stroke followed for a median duration of 12.9 years, overweight or obesity was associated with a more favourable prognosis for subsequent MACE, PVD, cardiovascular mortality, and all-cause mortality, irrespective of sex, diabetes mellitus, smoking, or cancer at time of incident stroke.

After the first reports of the stroke–obesity paradox,[22] several confirmatory reports were subsequently published.[23] The stroke–obesity paradox comes in contrast to the well-established association between obesity and risk of cardiovascular disease in the general population.[24] Different explanations were proposed to explain this paradoxical conclusion. It was suggested that this may simply represent an erroneous finding associated with methodology pitfalls like reverse causation, that is, low body weight may be an index for the presence of chronic diseases like cancer, malnutrition, infectious disease, smoking duration, and intensity, which in turn increase mortality.[25] For example, in a NHANES analysis, the obesity paradox was present among persons with dysglycaemia, but was absent in the subgroup of never-smokers.[26] To identify potential reverse causation in our analysis, we performed subgroup analyses in patients with and without diabetes mellitus, current smoking, and patients without cancer diagnosis at the time of incident stroke. In our cohort, diabetes mellitus was less prevalent

while current smoking and cancer were more prevalent in underweight patients. The stroke–obesity paradox was present irrespective of diabetes mellitus, smoking, or cancer at time of incident stroke. Although these findings do not support the explanation of reverse causation, still it may be possible that this might have occurred by other chronic illnesses that we did not consider in our analysis.

Another suggested explanation for the stroke–obesity paradox was residual confounding.[25] In our analysis, the results were adjusted for many prospectively registered patient characteristics like age, sex, socioeconomic status, comorbidities, and concurrent medication. We cannot exclude the possibility that additional unmeasured confounding bias might have been introduced, for example, comorbidities that are associated with cardiovascular outcomes, might have not been equally distributed among BMI strata. However, key comorbidities of cardiovascular risk are featured within the metabolic syndrome comprising hypertension, diabetes, hyperlipidaemia all well associated with excessive body weight. Those factors were well included in the multivariate adjusted assessments and—in accordance with common knowledge—a higher, not lower, prevalence of such comorbidities with higher body weight was observed in our study. Hence a higher risk profile of relevant cardiovascular risk factors may be concluded for patients with higher BMI.

Main strengths of this analysis can be seen in the large size of this prospective population-base cohort, the long duration of follow-up exceeding a decade, and the large number of outcome events. Moreover, to minimize the risk of bias due to residual confounding, the results were adjusted for a wide range of comorbidities and clinical covariates. Also, to identify potential reverse causal pathways, we performed subgroup analyses according to sex, diabetes, current smoking habit, and cancer (excluding those with a diagnosis) at the time of incident stroke. A limitation of the study was that BMI was the only marker of obesity that we analysed, as there were no available data about other anthropometric markers of obesity like waist-hip-ratio or waist circumference. Given that BMI is an imperfect marker of obesity, it would be interesting to see in other cohorts whether the obesity-paradox remains present when other markers of obesity are analysed. Moreover, combined models showed that within BMI groups, waist circumference can further stratify cardiovascular risk.[27,28] Finally, our analysis was not designed to assess the effect of weight management in stroke survivors as there were no available data on change of weight during follow-up. Recently, an analysis in the ORIGIN dataset identified weight loss an independent risk factor for higher mortality compared to no weight loss.[29]

From the restricted cubic spline plots, 23 and 25 kg/m^2 maybe better BMI cut-off points for increased or decreased risk of subsequent MACE and all-cause mortality outcomes respectively for this population-based study. These cut-offs will need to, however, be explored in other populations. It is important to note that the conclusions of this analysis as well as previous reports of the stroke–obesity paradox, should only be viewed as a putative association and should not be perceived as proof of causality. Therefore, no recommendations about weight management after stroke should be based on these conclusions. Ongoing randomized controlled trials might provide further evidence to guide weight management recommendations in stroke survivors. Semaglutide was recently associated with sustained, clinically relevant reduction in body weight[30] and is currently assessed for the reduction of cardiovascular events in patients with overweight or obesity and prior cardiovascular disease including stroke.[31]

Conclusions

In this prospective population-base cohort study of 30 702 patients with incident stroke followed for a median duration of 12.9 years, overweight or obesity was associated with a more favourable prognosis for subsequent MACE, PVD, and mortality, irrespective of sex, diabetes mellitus, smoking, or cancer at time of incident stroke.

Author Contributions

R. K. A. and G. N. were involved in the study conception. Analysis was performed by R. K. A. The manuscript was drafted by R. K. A. with support from G. N.

All authors reviewed and approved the final manuscript. RKA is the guarantor.

Acknowledgements

We thank the practices that contributed to the CPRD GOLD. The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[32]

Conflict of interest

R. K. A. currently holds an NIHR-SPCR funded studentship (2018-2021). S. W. is currently an employee of Janssen R&D.

Funding

R. K. A. is funded by a National Institute for Health Research School for Primary Care Research (NIHR SPCR) PhD

studentship award. The views expressed are those of the authors and not necessarily those of the NIHR, the NHS, or the Department of Health and Social Care.

Online supplementary material

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

Figure S1 Study flow diagram.
Figure S2 Distribution of body mass index in the study population.

Table S1 Number (proportion) of people with missing data on risk factors, by sex.
Table S2 Descriptive characteristics comparing patients with or within BMI record within 24 months of incident stroke.
Table S3 Descriptive characteristics of patients with body mass index record before incident stroke stratified by sex.
Table S4 Outcomes in body mass index subgroups presented by sex for fully adjusted model.
Table S5 Outcomes in body mass index subgroups presented by diabetes mellitus status for fully adjusted model.
Table S6 Outcomes in body mass index subgroups presented by smoking status for fully adjusted model.
Table S7 Outcomes in body mass index subgroups excluding patients with subsequent major adverse outcomes within 30 days of incident stroke (n = 21,967).

REFERENCES

1. Strazzullo P, D'Elia L, Cairella G, Garbagnati F, Cappuccio FP, Scalfi L. Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. *Stroke* 2010;**41**: e418–e426.
2. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, et al. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ* 2016;**353**: i2156.
3. Lopez-Jimenez F, Jacobsen SJ, Reeder GS, Weston SA, Meverden RA, Roger VL. Prevalence and secular trends of excess body weight and impact on outcomes after myocardial infarction in the community. *Chest* 2004;**125**:1205–1212.
4. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am College Cardiol* 2001;**38**:789–795.
5. 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**:666–678.
6. Wang ZJ, Zhou YJ, Galper BZ, Gao F, Yeh RW, Mauri L. Association of body mass index with mortality and cardiovascular events for patients with coronary artery disease: a systematic review and meta-analysis. *Heart* 2015;**101**:1631–1638.
7. Doehner W, Schenkel J, Anker SD, Springer J, Audebert H. Overweight and obesity are associated with improved survival, functional outcome, and stroke recurrence after acute stroke or transient ischaemic attack: observations from the tempis trial. *Eur Heart J* 2013;**34**:268–277.
8. Choi H, Nam HS, Han E. Body mass index and clinical outcomes in patients after ischaemic stroke in South Korea: a retrospective cohort study. *BMJ Open* 2019;**9**: e028880.
9. Dehlendorff C, Andersen KK, Olsen TS. Body mass index and death by stroke. *JAMA Neurol* 2014;**71**(8):978–984. http://doi.org/10.1001/jamaneurol.2014.1017
10. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol* 2015; **44**(3):827–836. https://doi.org/10.1093/ije/dyv098
11. NHS Digital. Hospital Episode Statistics (HES). NHS Digit. 2019https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics. Accessed 21 June 2019.
12. Office for National Statistics. Deaths registration data. ONS. 2018 https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths. Accessed 21 June 2019.
13. Department of Communities and Local Government. English indices of deprivation 2015. **1**:1–11.
14. Akyea RK, Vinogradova Y, Qureshi N, Patel RS, Kontopantelis E, Ntaios G, et al. Sex, age, and socioeconomic differences in nonfatal stroke incidence and subsequent major adverse outcomes. *Stroke* 2021; **52**:396–405.
15. Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, Van Staa T, Grundy E, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Bangkok)* 2014;**36**:684–692.
16. World Health Organization (WHO) Europe. Body mass index—BMI. https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi. Accessed 24 March 2021.
17. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. *New England J Med* 2010;**363**:2211–2219.
18. Kuan V, Denaxas S, Gonzalez-Izquierdo A, Direk K, Bhatti O, Husain S, et al. A chronological map of 308 physical and mental health conditions from 4 million individuals in the English National Health Service. *Lancet Digit Heal* 2019;**1**: e63–e77.
19. Mishra P, Pandey CM, Singh U, Gupta A, Sahu C, Keshri A. Descriptive statistics and normality tests for statistical data. *Annal Cardiac Anaesthesia* 2019;**22**:67–72.
20. Royston P. Multiple imputation of missing values: update of ice. *Stata J* 2005; **5**(4):527–536.
21. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Wiley; 1987. doi:10.1002/9780470316696.
22. Vemmos K, Ntaios G, Spengos K, Savvari P, Vemmou A, Pappa T, et al. Association between obesity and mortality after acute first-ever stroke. *Stroke* 2011;**42**(1):30–36. http://doi.org/10.1161/strokeaha.110.593434
23. Oesch L, Tatlisumak T, Arnold M, Sarikaya H. Obesity paradox in stroke ± myth or reality? A systematic review. *PLoS ONE* 2017;**12**:e0171334.
24. The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *New England J Med* 2017;**377**:13–27.
25. Tobias DK. Addressing reverse causation bias in the obesity paradox is not 'one size fits all'. *Diab Care* 2017;**40**: 1000–1001.
26. Preston SH, Stokes A. Obesity paradox: conditioning on disease enhances biases in estimating the mortality risks of obesity. *Epidemiology* 2014;**25**:454–461.
27. Zhu S, Heshka S, Wang ZM, Shen W, Allison DB, Ross R, et al. Combination of BMI and waist circumference for identifying cardiovascular risk factors in whites. *Obes Res* 2004;**12**:633–645.

28. Coutinho T, Goel K, Corrêa De Sá D, Carter RE, Hodge DO, Kragelund C, et al. Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease. *J Am College Cardiol* 2013;**61**(5):553–560. http://doi.org/10.1016/j.jacc.2012.10.035
29. Doehner W, Gerstein HC, Ried J, Jung H, Asbrand C, Hess S, et al. Obesity and weight loss are inversely related to mortality and cardiovascular outcome in prediabetes and type 2 diabetes: data from the ORIGIN trial. *Eur Heart J* 2020;**41**:2668–2677.
30. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. *New England J Med* 2021;**384**:989–1002.
31. Ryan DH, Lingvay I, Colhoun HM, Deanfield J, Emerson SS, Kahn SE, et al. Semaglutide effects on cardiovascular outcomes in people with overweight or obesity (SELECT) rationale and design. *Am Heart J* 2020;**229**:61–69.
32. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle*: update 2019. *J Cachexia Sarcopenia Muscle* 2019;**10**:1143–1145.