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Association between dynamic obesity and mortality in patients with first-ever ischemic stroke

A hospital-based prospective study

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Abstract

Although obesity is an established risk factor of primary stroke, the association between obesity and post-stroke mortality remains unclear. The aim of this study was to investigate the association between dynamic obesity status and mortality in survivors of their first stroke in China.

Of 775 patients with first-ever ischemic stroke included in a longitudinal study, 754 patients were included in this study and categorized into 4 categories of body mass index (BMI) (underweight, normal weight, overweight, and obese) and 2 categories of waist circumference (WC) (normal WC and abdominal obesity) according to standard Chinese criteria. The mortality information and obesity status were obtained via telephone follow-up every 3 months, beginning in 2010 through 2016. Time-dependent Cox proportional hazards models were used to estimate the unadjusted and adjusted hazard ratios (HRs) for the relationship between all-cause mortality and dynamic obesity status.

Of 754 patients, 60.87% were male, and the overall mean age was 61.45 years. After adjusting for possible confounders, significant inverse associations were identified between BMI and WC and all-cause mortality. Compared with those with normal BMI or WC, those with abdominal obesity or overweight had a significantly lower risk of all-cause mortality (HR and 95% confidence intervals [CIs]: .521 [.303–.897] and 0.545 [.352–.845], respectively), whereas patients with underweight had the highest risk and those with obesity had lower risk of mortality, though it was not statistically significant (1.241 [.691–2.226] and .486 [.192–1.231], respectively).

Overweight and abdominal obesity were paradoxically associated with reduced risk of mortality in patients who survived their first-ever ischemic stroke in China. Future prospective studies must look at evaluating the role of obesity in different stroke subtypes and devise appropriate weight-management strategies for optimal prognoses in secondary prevention in these survivors.

Abbreviations: BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, HR = hazard ratio, IL = interleukin, mRS = modified Rankin Scale, OCSP = Oxfordshire Community Stroke Project, TEMPiS = Telemedical Project for Integrative Stroke Care, TOAST = Org 10172 in Acute Stroke Treatment, WC = waist circumference.

Keywords: ischemic stroke, mortality, obesity, paradox, time-dependent

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The authors declare that they have no competing interests.

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1. Introduction

Obesity has become a global epidemic and a major public health concern.[1–3] The prevalences of overweight and obesity in adults older than 18 years of age in 2016 were approximately 39% and 13% worldwide, respectively.[4] Epidemiological studies have demonstrated that obesity is a risk factor for hypertension,[5] diabetes mellitus (DM),[6] atrial fibrillation,[7] certain cancers,[8,9] major cardiovascular diseases,[10,11] stroke,[12] and total mortality in the general population. Accordingly, the general agreement is to recommend striving for a normal weight as part of primary prevention of stroke.[13] However, the latest guidelines for secondary prevention suggest that the beneficial effects of reducing weight remain uncertain.[14] Furthermore, the association of obesity with mortality in patients with stroke remains controversial. Some findings suggest that obesity worsens the prognosis in survivors of stroke,[15,16] while others suggest that obesity confers better survival.[13,17] Numerous findings indicate that, in contrast to the general population, an inverse relationship is present between obesity and mortality in survivors of stroke, which is termed as obesity paradox.[18,19] Andersen et al[13] analyzed 45,615 patients with acute first-ever stroke (irrespective of the subtype of stroke), and concluded that obesity was not only associated with reduced mortality but also with lower risk of readmission for recurrent stroke relative to patients with normal weight. In the Telemedical Project for Integrative Stroke Care (TEMPiS) study that included data of 4,428 patients with acute stroke or transient ischemic attack, the highest mortality was observed in underweight patients.[17] Therefore, patients with overweight and obesity demonstrated significantly better survival than did patients with normal body weight. Therefore, it is unclear if the recommendations of primary prevention should be extended to secondary prevention of cardiovascular diseases as well.

Previous studies on the paradox between obesity and stroke outcomes have limitations. Therefore, the results are yet to be confirmed. It is well known, however, that the assumption that obesity status remains constant during follow-up is unreasonable, which may result in misclassification of the obesity status and possibly biased results. Furthermore, it is noteworthy that numerous studies on the obesity paradox fail to fully consider the confounders associated with all-cause mortality in post-stroke patients—e.g., the stroke severity may not have been quantified and the treatment of stroke was ignored[13,16] —which may provide a false impression that obesity constitutes a survival advantage.

Therefore, the question remains if the phenomena that obesity is associated with better prognosis after stroke is true or is it biased by imperfect adjustments for confounders and research methodology? Is maintaining normal weight still advisable if being overweight or obese confers more favorable prognoses? To our best of knowledge, few studies have simultaneously used body mass index (BMI) and waist circumference (WC) to describe the obesity status in patients with stroke from the general and abdominal obesity aspects, and few studies have considered the dynamic obesity status. Furthermore, limited studies have explored the relationship between obesity and post-stroke mortality in the Chinese population, a subgroup with high prevalence rates of obesity and stroke.[20,21] Therefore, the aim of our study was to investigate the association between dynamic obesity status and mortality in survivors of first-ever ischemic stroke in China.

2. Patients and methods

2.1. Study population

The study was performed in the Department of Neurology, West China Hospital. The diagnosis of stroke was established according to the World Health Organization criteria.[22] Survivors of first-ever ischemic stroke were screened by computed tomography or magnetic resonance imaging. Patients who underwent cardiovascular surgeries, such as carotid endarterectomy, cardiac surgeries, or angiography, which may induce stroke, were excluded.

2.2. Ethics statements

Written informed consents were obtained from all patients or their designated relatives. The study protocol was approved by the Ethics Committee of the West China Hospital, Sichuan University, Chengdu, China (ethical approval number, "2009 year 50").

2.3. Study design

A semi-structured questionnaire was used to conduct face-to-face interviews in the hospital by professionally trained, qualified, and experienced interviewers. The interviewers consisted of students pursuing Masters in Public Health who studied clinical medicine for 5 years as an undergraduate and had sufficient clinical expertise. The face-to-face interview was supplemented by medical records. The demographic characteristics included sex, age (<45, 45–64, and >65 years), marital status (with spouse, without spouse), occupation (farmer, non-agricultural laborer, retired, and unemployed), education (≤6, 7–9, and ≥10 years), household income (<$3057.4, $3057.4–6114.8, and >$6114.8 per year), and number of family members (<3, 3–4, and >4 persons). Lifestyle parameters included smoking status (never smoked, cessation of smoking, currently smoking, and passively smoking), drinking status (never or current drinking), and pre-stroke exercise duration (<210, 210–420, and >420 minutes per week). Vascular risk factors included family history of stroke, hypertension, DM, hyperlipidemia, heart disease, and peripheral vascular diseases. The aforementioned comorbidities were diagnosed as per the current standards.[23,24]

2.4. Measure of obesity

Most patients were unable to stand on admission; therefore, it was difficult to directly measure their height, weight, and WC. At baseline, the participants were asked to report their weight, height, and WC by answering the following questions: "what is your weight now?" (in kg to the nearest .1 kg) and "what is your height and waist circumference?" (in cm to the nearest .1 cm).

According to the distribution of fat, obesity is divided into general obesity (i.e., obesity) and abdominal obesity.[25,26] Obesity is assessed according to BMI, and abdominal obesity is commonly assessed according to WC. BMI is calculated by dividing the body weight (kg) by height squared (meters). WC refers to the circumference at a point midway between the lowest rib and the iliac crest in the horizontal plane.

Overweight, general obesity, and abdominal obesity were defined by the standard criteria for the Chinese population (underweight: BMI <18.5 kg/m^2; normal weight: BMI, 18.5 to <24 kg/m^2; overweight: BMI, 24–28 kg/m^2; general obesity: BMI

>28 kg/m^{2}[24,27]; abdominal obesity: WC ≥85 cm for men and ≥80 cm for women[28,29]).

2.5. Outcomes and follow-up

Follow-up was routinely performed via telephone interviews every 3 months by trained and qualified investigators after hospital discharge. Before formal participation in the survey, the project organizer held a training meeting for investigators about standardization of the survey language and matters that required attention. The follow-up survey included information regarding the severity of stroke, body weight, WC, adherence to anti-thrombotic medications, and health outcomes. Most patients were in the acute phase at the time of the baseline survey, and stroke severity changes quickly; thus, the modified Rankin Scale (mRS) scores at the time of the baseline survey may not accurately reflect the stroke severity.[30] Therefore, the mRS score at the first follow-up was deemed to indicate the stroke severity instead. mRS score <2 was defined as mild disability, whereas mRS score ≥3 was defined as severe/moderate disability.[31] Strict adherence of patients to anti-thrombotic medications or to alterations of the pharmacotherapy according to the doctors advice during the follow-up period was termed as adherence. The endpoint of the study was all-cause mortality, which was obtained from the patients relatives during follow-ups. Survival time was calculated from the baseline survey until death due to any cause, withdrawal from the study, or the last follow-up since June 2016.

2.6. Statistical analysis

Descriptive statistics of the baseline individual characteristics were stratified based on the baseline obesity status as assessed by BMI and WC using the Chi-Squared test or Fisher exact test. We used change in obesity status, which was updated every 3 months, as a time-varying exposure, and a time-dependent Cox proportional hazard regression model[32,33] was used to estimate the hazards ratio (HR) for all-cause mortality during the follow-up. In this study, both empirical and theoretical strategies were considered for the chosen confounding factors.[34] Statistical tests were two-sided, and a *P* value <.05 was considered statistically significant. All statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

Between January 2010 and June 2016, 775 participants were enrolled. After excluding 21 patients (2.7%) because of duplication and missing data, 754 patients were included in our analysis. The overall mean age was 61.45 years (range, 17–89 years) and 60.88% were male. The included patients were followed up for a mean period of 54.86 months (range, 0–75 months). The baseline demographic and clinical characteristics are summarized in Table 1.

At admission, 33.69% of patients were categorized as overweight, 10.08% as obese, and 45.62% to have abdominal obesity; the survival curve differed significantly between the subgroups (Figs. 1 and 2). Results of the univariate analysis are summarized in Table 2.

Results of the multivariable-adjusted time-dependent Cox proportional hazards regression analysis of the BMI and WC subgroups are summarized in Tables 3 and 4, respectively. When adjusted for only age, overweight was associated with lower mortality compared with the other BMI categories (HR: .491, 95% confidence interval [CI]: .293–.824); in the univariate analysis, the severity of stroke was strongly associated with post-stroke mortality. After age and stroke severity were simultaneously adjusted, the results of overweight differed slightly (HR: .506; 95% CI: .302–.850). Similarly, after simultaneous adjustments for all socio-demographic and other factors presented in Table 2, an inverse relationship between BMI and all-cause mortality was constantly observed in those who were overweight (HR: .521; 95% CI: .303–.897). Particularly, those were underweight had the worst survival constantly in all the adjusted models; however, they were not statistically significant. Notably, in those who were obese, the statistical significance was lost after adjustments were made for any of the listed confounders. After simultaneous adjustments were made for all of the aforementioned factors, the significant association between mortality and obesity was still not observed (HR: .487; 95% CI: .192–1.235).

Furthermore, regarding the threshold categories for WC, the inverse association was constantly observed in all of the considered models. Following simultaneous adjustments for all of the characteristics, the mortality risk was significantly lower in those with abdominal obesity than in those with normal WC (HR: 572; 95% CI: 370–883).

4. Discussion

The main finding of present study is that patients hospitalized for ischemic stroke who were overweight and obese had better survival than those who were normal weight. In contrast, patients who were underweight demonstrated the worst mortality rates. It is noteworthy that the inverse association between body weight and outcome measures remained after adjustments for confounders. Furthermore, the inverse association between abdominal obesity and mortality was also constantly observed.

The results of this study are in line with those of studies that demonstrated that overweight was associated with a significantly lower risk of mortality.[35,36] When omitting different covariates from our models, the risk of mortality in those who were overweight remained low. Similarly, Vemmos et al[36] revealed that patients who were overweight had significantly better survival rates than those with normal BMI. In contrast, inconsistent with our findings, Dehlendorff et al[37] suggested that being overweight was not associated with decreased risk of all-cause mortality. The possible reason for this difference is that survivors of both ischemic stroke and hemorrhagic stroke were included in their study while we only included the former. Another possible explanation for the distinct results is that our participants were followed up for a mean period of 54.86 months and the endpoint was all-cause mortality; the outcomes in the study by Dehlendorff et al were deaths due to index stroke at 1 week and 1 month.

Furthermore, our findings revealed that obesity confers a lower risk of mortality without statistical significance, which is consistent with those of previous studies.[38,39] A Chinese follow-up study[40] found that obesity (BMI, 27.5–32.4 kg/m^{2}) was not associated with increased risk of mortality, which is similar to the South Korean results by Ryu et al.[38] However, the TEMPiS study[17] revealed that the lowest mortality risk was observed in obese and very obese patients and not in those with normal BMI. The discrepancy in the findings may be due to several reasons. Firstly, the TEMPiS study was a non-randomized intervention study that compared acute stroke treatment without

Table 1

Epidemiologic characteristics, co-morbidities, and stroke severity by BMI and WC subgroup (at admission).

		BMI Category					WC Category		
Characteristics	Total	Underweight (N,%)	Normal weight (N,%)	Overweight (N,%)	Obese (N,%)	*P* value	Normal WC (N,%)	Abdominal obesity (N,%)	*P* value
Number of participant (N,%)	754	49 (6.50)	375 (49.73)	254 (33.69)	76 (10.08)		344 (45.62)	410 (54.38)	
Sex									
Male	459	27 (5.88)	234 (50.98)	154 (33.55)	44 (9.59)	.719	218 (47.49)	241 (52.51)	.198
Female	295	22 (7.46)	141 (47.80)	100 (33.90)	32 (10.85)		126 (42.71)	169 (57.29)	
Age-group(year)*									
<45	84	4 (4.76)	43 (51.19)	24 (28.57)	13 (15.48)	.207	43 (51.19)	41 (48.81)	.446
45–	337	19 (5.64)	158 (46.88)	125 (37.09)	35 (10.39)		156 (46.29)	181 (53.71)	
65–	332	26 (7.83)	174 (52.41)	104 (31.33)	28 (8.43)		145 (43.67)	187 (56.33)	
Married status									
Without spouse	96	12 (12.50)	51 (53.13)	22 (22.92)	11 (11.46)	.016	43 (44.79)	53 (55.21)	.861
With spouse	658	37 (5.62)	324 (49.24)	232 (35.26)	65 (9.88)		301 (45.74)	357 (54.26)	
Education(year)*									
≤6	285	26 (9.12)	142 (49.82)	89 (31.23)	28 (9.82)	.364	138 (48.42)	147 (51.58)	.282
7 to 9	190	7 (3.68)	95 (50.00)	69 (36.32)	19 (10.00)		88 (46.32)	102 (53.68)	
≥10	275	16 (5.82)	135 (49.09)	96 (34.91)	28 (10.18)		115 (41.82)	160 (58.18)	
Occupation*									
Farmer	189	16 (8.47)	101 (53.44)	59 (31.22)	13 (6.88)	.326	98 (51.85)	91 (48.15)	.047
Non-agricultural laborer	203	10 (4.93)	101 (49.75)	66 (32.51)	26 (13.30)		100 (49.26)	103 (50.74)	
Retired	312	17 (5.45)	151 (48.40)	112 (35.90)	32 (12.81)		126 (40.38)	186 (59.62)	
Unemployed	49	6 (12.24)	22 (44.90)	17 (34.69)	4 (8.16)		20 (40.82)	29 (59.18)	
Household income (dollars/year)*									
< 3057.4	252	22 (8.73)	129 (51.19)	83 (32.94)	18 (7.14)	.451	129 (51.19)	123 (48.81)	.058
3057.4 to 6114.8	245	13 (5.31)	121 (49.39)	84 (34.29)	27 (11.02)		110 (44.90)	135 (55.10)	
> 6114.8	237	14 (5.91)	113 (47.68)	83 (35.02)	27 (11.39)		96 (40.51)	141 (59.49)	
Number of resident population									
< 3	359	27 (7.52)	182 (50.70)	118 (32.87)	32 (8.91)	.780	158 (44.01)	201 (55.99)	.690
3 to 4	249	13 (5.22)	118 (47.39)	89 (35.74)	29 (11.65)		118 (47.39)	131 (52.61)	
> 4	146	9 (6.16)	75 (51.37)	47 (32.19)	15 (10.27)		68 (46.58)	78 (53.42)	
Smoking status									
Non-smoking	334	23 (6.89)	161 (48.20)	108 (32.34)	42 (12.57)	.139	144 (43.11)	190 (56.89)	.403
Passive smoking	117	7 (5.98)	54 (46.15)	49 (41.88)	7 (5.98)		51 (43.59)	66 (56.41)	
Smoking cessation	244	15 (6.15)	125 (51.23)	85 (34.84)	19 (7.79)		122 (50.00)	122 (50.00)	
Current smoking	59	4 (6.78)	35 (59.32)	12 (20.34)	8 (13.56)		27 (45.76)	32 (54.24)	
Drinking status									
Non-drinking	490	34 (6.94)	242 (49.39)	170 (34.69)	44 (8.98)	.466	209 (42.65)	281 (57.35)	.026*
Current drinking	264	15 (5.68)	133 (50.38)	84 (31.82)	32 (12.12)		135 (51.14)	129 (48.86)	
Pre-stroke exercise time within a month a week (minutes)									
<210 minutes	491	30 (6.11)	255 (51.93)	156 (31.77)	49 (9.99)	.001	229 (46.64)	262 (53.36)	.194
210 –	82	14 (17.07)	34 (41.46)	26 (31.71)	8 (9.76)		42 (51.22)	40 (48.78)	
420 –	181	5 (2.76)	85 (46.96)	72 (39.78)	19 (10.50)		73 (40.33)	108 (59.67)	
Stroke severity									
Mild disability	486	22 (4.53)	240 (49.38)	170 (34.98)	54 (11.11)	.016	225 (46.30)	261 (53.70)	.617
Severe/Moderate disability	268	27 (10.07)	135 (50.37)	84 (31.34)	22 (8.21)		119 (44.40)	149 (55.60)	
Family history of stroke									
No	606	39 (6.44)	312 (51.49)	200 (33.00)	55 (9.08)	.143	290 (47.85)	316 (52.15)	.013
Yes	148	10 (6.76)	63 (42.57)	54 (36.49)	21 (14.19)		54 (36.49)	94 (63.51)	
Hypertension									
No	284	25 (8.80)	157 (55.28)	86 (30.28)	16 (5.63)	.001	155 (54.58)	129 (45.42)	<.001
Yes	470	24 (5.11)	218 (46.38)	168 (35.74)	60 (12.77)		189 (40.21)	281 (59.79)	
Diabetes mellitus									
No	552	42 (7.61)	294 (53.26)	166 (30.07)	50 (9.06)	<.001	280 (50.72)	272 (49.28)	<.001
Yes	202	7 (3.47)	81 (40.10)	88 (43.56)	26 (12.87)		64 (31.68)	138 (68.32)	
Hyperlipidemia*									
No	486	41 (8.44)	269 (55.35)	140 (28.81)	36 (7.41)	<.001	248 (51.03)	238 (48.97)	<.001
Yes	266	8 (3.01)	104 (39.10)	114 (42.86)	40 (15.04)		94 (35.34)	172 (64.66)	
Heart disease									
No	587	36 (6.13)	288 (49.06)	204 (34.75)	59 (10.05)	.641	275 (46.85)	312 (53.15)	.205
Yes	167	13 (7.78)	87 (52.10)	50 (29.94)	17 (10.18)		69 (41.32)	98 (58.68)	
Peripheral vascular diseases*									
No	732	47 (6.42)	365 (49.86)	246 (33.61)	74 (10.11)	0.768	336 (45.90)	396 (54.10)	.479
Yes	21	2 (9.52)	9 (42.86)	8 (38.10)	2 (9.52)		8 (38.10)	13 (61.90)	
Anti-thrombotic drug medication adherence									
Adherence	306	18 (5.88)	156 (50.98)	99 (32.35)	33 (10.78)	.804	138 (45.10)	168 (54.90)	.811
Non-adherence	448	31 (6.92)	219 (48.88)	155 (34.60)	43 (9.60)		206 (45.98)	242 (54.02)	

* For some socio-demographic characteristics the sample size did not add up to 754 due to missing value.

P by χ^2 test or Fisher exact test.

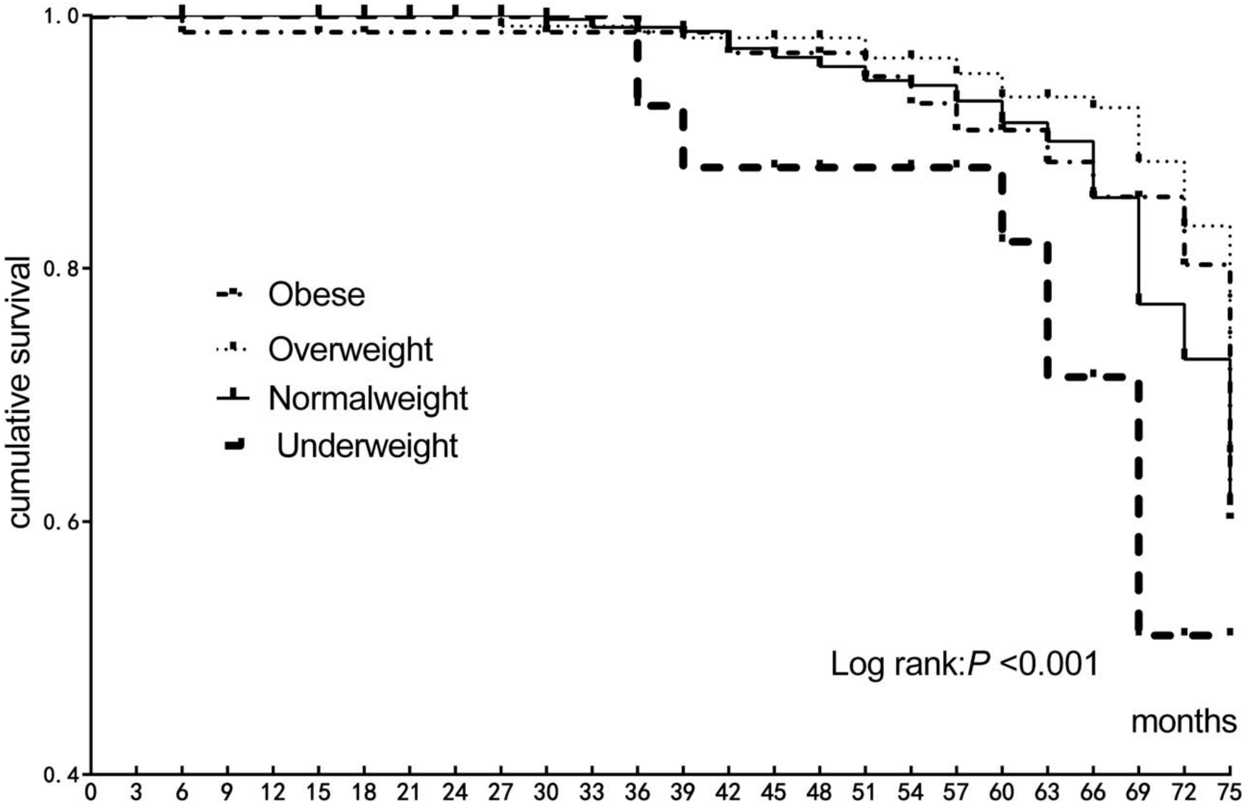

Figure 1. Survival curves following stroke according to groups of body mass index (BMI; univariate analysis).

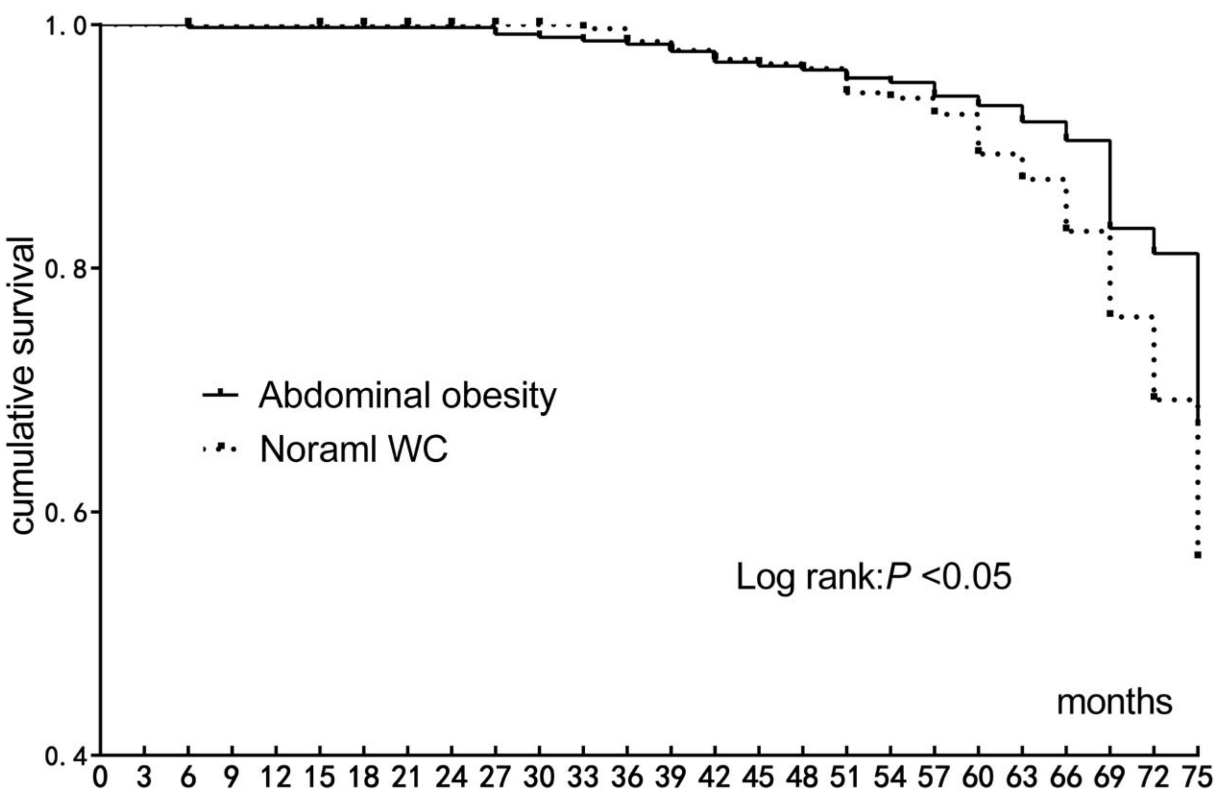

Figure 2. Survival curves following stroke according to groups of waist circumference (WC; univariate analysis).

Table 2

Relationship between BMI, WC and related factors with all-cause mortality in unadjusted analysis.

Parameter	HR	95%CI	*P* value
BMI criteria			
Normal weight (18.5 to <24)	1.000 (reference)		
Underweight (<18.5)	1.554	(0.895,2.700)	.118
Overweight (24 to <27.9)	0.456	(0.272,0.764)	.003
Obese (≥28.0 kg/m^2)	0.370	(0.148,0.921)	.033
WC criteria			
Normal WC(male and WC ≤85 cm or female WC ≤80 cm)	1.000 (reference)		
Abdominal obesity(male and WC >85 cm or female WC >80 cm)	0.527	(0.352,0.790)	.002
Sex			
Male	1.000 (reference)		
Female	1.125	(0.756,1.674)	.561
Age-group (year)*			
<45	1.000 (reference)		
45–	2.403	(0.734,7.860)	.147
65–	5.501	(1.729,17.498)	.004
Marital status			
Without spouse	1.000 (reference)		
With spouse	0.455	(0.287,0.719)	.001
Education (year)*			
≤6	1.000 (reference)		
7 to 9	0.446	(0.258,0.770)	.004
≥10	0.554	(0.352,0.871)	.011
Occupation*			
Farmer	1.000 (reference)		
Non-agricultural laborer	0.265	(0.126,0.555)	<.001
Retired	0.970	(0.626,1.505)	.894
Unemployed	0.678	(0.283,1.621)	.382
House hold income (dollars/year)*			
< 3057.4	1.000 (reference)		
3057.4 to 6114.8	1.006	(0.638,1.587)	.980
> 6114.8	0.824	(0.497,1.366)	.452
Number of resident population			
< 3	1.000 (reference)		
3 to 4	0.716	(0.45,1.138)	.157
> 4	0.886	(0.53,1.482)	.646
Smoking status			
Non-smoking	1.000 (reference)		
Passive smoking	0.593	(0.324,1.085)	.090
Smoking cessation	0.600	(0.377,0.955)	.031
Current smoking	0.617	(0.247,1.542)	.302
Drinking status			
Non-drinking	1.000 (reference)		
Current drinking	0.603	(0.386,0.943)	.027
Pre-stroke exercise time within one week (minutes)			
<210	1.000 (reference)		
210 –	1.030	(0.546,1.944)	.928
420 –	0.750	(0.442,1.273)	.286
Stroke severity			
Mild disability	1.000 (reference)		
Severe/Moderate disability	4.155	(2.767,6.239)	<.001
Family history of stroke			
No	1.000 (reference)		
Yes	0.708	(0.415,1.209)	.206
Hypertension			
No	1.000 (reference)		
Yes	0.890	(0.595,1.330)	.569
Diabetes mellitus			
No	1.000 (reference)		
Yes	1.158	(0.752,1.785)	.505
Hyperlipidemia*			
No	1.000 (reference)		
Yes	0.683	(0.445,1.049)	.081
Heart disease			
No	1.000 (reference)		
Yes	1.387	(0.896,2.147)	.142
Peripheral vascular diseases*			
No	1.000 (reference)		
Yes	0.965	(0.306,3.043)	.951
Anti-thrombotic drug medication adherence			
Adherence	1.000 (reference)		
Non-adherence	0.766	(0.512,1.147)	.196

* For some socio-demographic characteristics the sample size did not add up to 754 due to missing values.

CI = confidence interval, HR = hazard ratio.

Table 3

Effects of adjustment for personal characteristics and various indices of health on the association between all-cause mortality and BMI criteria.

All patients	Underweight		Overweight		Obese	
P and HR (95% CI) of all-cause mortality as normal BMI as reference, adjusted for:	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)
Age only	.120	1.549 (0.892,2.692)	**.007**	0.491 (0.293,0.824)	.068	0.427 (0.171,1.067)
Age and mRS‡	.382	1.281 (0.735,2.233)	**.010**	0.506 (0.302,0.850)	.073	0.433 (0.174,1.082)
Age, mRS‡ and personal characteristics*	.586	1.173 (0.661,2.078)	**.011**	0.507 (0.299,0.858)	.131	0.489 (0.194,1.236)
Age, mRS‡, personal characteristics* and comorbidities†	.650	1.144 (0.640,2.044)	**.019**	0.523 (0.304,0.898)	.129	0.487 (0.192,1.233)
Age, mRS‡, personal characteristics*, comorbidities† and and anti-thrombotic medication adherence	.632	1.153 (0.644,2.062)	**.019**	0.523 (0.305,0.897)	.130	0.487 (0.192,1.235)

* personal characteristics include sex, married status, occupation, education, annual household income, number of resident population in their family, smoking status, drinking status, pre-stroke exercise time.
† Comorbidity included hypertension, diabetes mellitus, hyperlipidemia, heart disease, peripheral vascular diseases.
‡ mRS: modified Rankin Scale.
CI = confidence interval, HR = hazard ratio.

specialized care for stroke in hospitals, while ours was a hospital-based longitudinal study without any interventions. Secondly, the TEMPiS study included individuals with hemorrhagic stroke as well, whereas our study included only those with the first incidence of ischemic stroke. Therefore, the relationship between obesity and all-cause mortality remains to be validated.

A remarkable finding in our study was that abdominal obesity was also associated with better prognoses in patients with stroke, which was in accordance with the results of previous studies.[41] However, the participants in the current study were divided into normal WC and abdominal obesity according to sex-specific WC criteria, which cannot distinguish between mild, moderate, and extreme abdominal obesity. However, Gomes et al[41] used quartiles of WC to categorize different levels of abdominal obesity; they found that patients in the 4th quartile of WC had significantly better survival, while those in the 3rd and 2nd quartiles had decreased risks of mortality without significance compared with those in the 1st quartile.

Our findings suggest that the beneficial effects of higher BMI and WC on all-cause mortality appear to be present in patients with the first episode of ischemic stroke, which was previously termed as obesity paradox.[42] The inverse relationship was also confirmed in different patient populations, such as those with heart failure,[43] those on dialysis,[44] and those with diabetes,[45,46] certain cancers,[47,48] atrial fibrillation,[49] and coronary artery bypass surgery.[50] A few explanations have been proposed for the paradox. Firstly, individuals may receive different treatments. As previously noted, obese patients who develop stroke demonstrate a readily identifiable high cardiovascular risk phenotype. Therefore, they may tend to present earlier or receive more aggressive treatment, thus, varying the natural history of their disease[51] and confer them with benefits of lead-time bias.[39] Similarly, Park et al[51] found that obese patients had a higher number of diagnosed medical comorbidities, were taking more medications, and had a higher rate of optimal combination drug treatment than lean patients, which could have contributed the differences in the prognoses. Secondly, obesity may affect the immune response and alter the levels of inflammatory factors.[52–55] Previous studies have reported that obese patients have lower levels of several proinflammatory cytokines, particularly interleukin (IL)-6 and IL-8. Additionally, obese individuals may be better equipped to undergo the initial catabolic phase of acute illness due to the additional energy stores in the form of lipoproteins and adipose tissue, which can neutralize the inflammatory effects.[52,56] Thirdly, obesity can worsen the symptoms, such as dyspnea, and obese individuals may have better prognosis because they present earlier with any specific disease.[57] High BMI may also be associated with some protective factors.[58] Another possible explanation is that relative to patients with normal weight, overweight/obese patients may have a better metabolic reservoir —an aspect that enables them to deal better with catabolic imbalance and impaired metabolic efficiency induced by stroke.[59] Alternatively, obese patients who have survived until their event may somehow be healthier individuals or have metabolically benign obesity.[60] Finally, obese patients are encouraged to change their unhealthy lifestyle [13] for a better prognosis; however, additional research is required in this regard.

Table 4

Effects of a djustment for personal characteristics and various indices of health on the association between all-cause mortality and WC criteria.

All patients	Abdominal obesity	
P and HR (95% CI) of all-cause mortality as normal WC as reference, adjusted for:	*P*	HR (95% CI)
Age only	**.003**	0.539 (0.359,0.807)
Age and mRS‡	**.002**	0.528 (0.352,0.793)
Age, personal characteristics* and mRS‡	**.005**	0.547 (0.360,0.832)
Age, personal characteristics*, mRS‡ and comorbidities†	**.011**	0.569 (0.368,0.880)
Age, personal characteristics*, mRS‡, comorbidities† and anti-thrombotic medication adherence	**.012**	0.572 (0.370,0.883)

* personal characteristics include sex, married status, occupation, education, annual household income, number of resident population in their family, smoking status, drinking status, pre-stroke exercise time.
† Comorbidity included hypertension, diabetes mellitus, hyperlipidemia, heart disease, peripheral vascular diseases.
‡ mRS: modified Rankin Scale.
CI = confidence interval, HR = hazard ratio.

Additionally, underweight may be the result of other underlying diseases, unintentional weight loss, reduced mental and physical health, or severe comorbidities that result in poor prognosis.[61,62]

Several strengths and limitations of this study should be acknowledged and discussed. The strength is that we considered the association of mortality with not only general obesity but also with abdominal obesity in a long-term Chinese cohort. Furthermore, important confounding factors, such as stroke severity and anti-thrombotic medication adherence, were comprehensively considered, which were often absent in previous studies.[13,16] Importantly, dynamic changes in weight and WC during the follow-up were also considered by recording BMI and WC at every follow-up, which may constitute for stronger conclusions.

Our study does have some limitations. Firstly, the weight, height, and WC were based on self-reporting by patients rather than by using objective tools, which may have resulted in biases.[63] However, previous studies have suggested that self-reported weight, height, and WC are satisfactorily accurate in the assessment of obesity status and have near-perfect correlations and agreement with the measured anthropometric values.[64,65] Furthermore, BMI fails in distinguishing between individuals with different types of fat distribution,[66] and WC is incapable of distinguishing between persons of varying heights.[67] However, directly and accurately quantified methods are impractical and time-consuming.[68] Therefore, self-reported data should be generally acceptable. Secondly, we could not include the subtypes of stroke because the necessary stroke etiology and clinical features for classification of the subtypes of stroke were insufficiently collected in first interview. Neither the TOAST (Org 10172 in Acute Stroke Treatment) nor Oxfordshire Community Stroke Project classification of the subtypes of stroke was obtained. Thirdly, index bias may be present in our study because though all possible confounding factors were considered, essentially perfect controlling for confounding factors between obesity and mortality is possible.[69] Even though unmeasured confounders are inevitable, index bias alone may be a partial explanation for the obesity paradox, which cannot deny the presence of obesity paradox in stroke survivors.[70] Finally, our participants were recruited from only the West China Hospital of Sichuan University, which may limit the generalizability of these findings.

5. Conclusions

Overweight and abdominal obesity were paradoxically associated with a lower risk of mortality in survivors of their first episode of ischemic stroke in China. Consequently, we suggest that the recommendations regarding body weight management in the secondary stroke pre-strategy should not simply refer to primary prevention. Future prospective studies must look at evaluating the role of obesity in different stroke subtypes and devise appropriate weight-management strategies for optimal prognoses in secondary prevention in these survivors.

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References

[1] Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009;53:1925–32.
[2] Huang K, Liu F, Han X, et al. Association of BMI with total mortality and recurrent stroke among stroke patients: a meta-analysis of cohort studies. Atherosclerosis 2016;253:94–101.
[3] Hyppönen E, Mulugeta A, Zhou A, et al. A data-driven approach for studying the role of body mass in multiple diseases: a phenome-wide registry-based case-control study in the UK Biobank. Lancet Digital Health 2019;1:e116–26.
[4] World Health Organization.Obesity and Overweight.World Helath Organization web site [cited 2020 Jun 1]; Available from: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight
[5] Toyama M, Watanabe S, Miyauchi T, et al. Diabetes and obesity are significant risk factors for morning hypertension: from Ibaraki Hypertension Assessment Trial (I-HAT). Life Sci 2014;104:32–7.
[6] Găman MA, Epîngeac ME, Diaconu CC, et al. Evaluation of oxidative stress levels in obesity and diabetes by the free oxygen radical test and free oxygen radical defence assays and correlations with anthropometric and laboratory parameters. World J Diabetes 2020;11:193–201.
[7] Gaman M, Dobrica E, Pascu EG, et al. Cardio metabolic risk factors for atrial fibrillation in type 2 diabetes mellitus: focus on hypertension, metabolic syndrome and obesity. J Mind Med Sci 2019;6:157–61.
[8] James FR, Wootton S, Jackson A, et al. Obesity in breast cancer – what is the risk factor? Eur J Cancer 2015;51:705–20.
[9] Karimi K, Lindgren TH, Koch CA, et al. Obesity as a risk factor for malignant melanoma and non-melanoma skin cancer. Rev Endocr Metab Disord 2016;17:389–403.
[10] Raza Q, Doak C, Khan A, et al. Obesity and cardiovascular disease risk factors among the indigenous and immigrant pakistani population: a systematic review. Obes Facts 2013;6:523–35.
[11] Chen Y, Copeland W, Vedanthan R, et al. Association between body mass index and cardiovascular disease mortality in East Asians and South Asians: pooled analysis of prospective data from the Asia Cohort Consortium. BMJ 2013;347:347f5446.
[12] Pasquale , Strazzullo , Lanfranco , et al. Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. Stroke J Cerebral Circul 2010;41:e418–26.
[13] Andersen KK, Olsen TS. The obesity paradox in stroke: lower mortality and lower risk of readmission for recurrent stroke in obese stroke patients. Int J Stroke 2015;10:99–104.
[14] Meschia JF, Bushnell C, Bodenalbala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American stroke association. Stroke 2014;45:3754–832.
[15] Karri S, Per T, Finn R. Weight status in young adulthood and survival after cardiovascular diseases and cancer. Int J Epidemiol 2014;43: 1197–204.
[16] Silventoinen K, Tynelius P, Rasmussen F. Weight status in young adulthood and survival after cardiovascular diseases and cancer. Int J Epidemiol 2014;43:1197–204.
[17] Doehner W, Schenkel J, Anker SD, et al. 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;34:268–77.

[18] Katsnelson M, Rundek T. Obesity paradox and stroke. Stroke 2011;42:3331–2.
[19] Mcauley PA, Blair SN. Obesity paradoxes. J Sports Sci 2011;29:773–82.
[20] Wang W, Jiang B, Sun H, et al. Prevalence, incidence, and mortality of stroke in China. Circulation 2017;135:759–72.
[21] Zhang J, Wang H, Wang Z, et al. Prevalence and stabilizing trends in overweight and obesity among children and adolescents in China, 2011-2015. BMC Public Health 2018;18:571.
[22] listed Na. Stroke-1989Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders Stroke. J Cerebral Circ 1989;20:1407–31.
[23] Kernan W, Ovbiagele B, Black H, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:216–36.
[24] Sun W, Huang Y, Xian Y, et al. Association of body mass index with mortality and functional outcome after acute ischemic stroke. Sci Rep 2017;7:2507.
[25] Anna Welcome, FACOG.Definition of Obesity; Obesity Medicine Association web site [cited 2020 June 1]; Available from: https://obesitymedicine.org/definition-of-obesity/
[26] Xi B, Liang Y, He T, et al. Secular trends in the prevalence of general and abdominal obesity among Chinese adults, 1993–2009. Obes Rev 2012;13:287–96.
[27] Beifan Z. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults–study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Biomed Environ Sci 2002;15:83–96.
[28] Lu B, Yang Y, Song X, et al. An evaluation of the International Diabetes Federation definition of metabolic syndrome in Chinese patients older than 30 years and diagnosed with type 2 diabetes mellitus. Metabolism 2006;55:1088–96.
[29] Zhai Y, Zhao WH, Chen C. Verification of the cut-off waist circumference for defining central obesity in Chinese adults. Int J Cardiol 2009;137:S101–2.
[30] Dong YH, Slavin MJ, Chan PL, et al. Cognitive screening improves the predictive value of stroke severity scores for functional outcome 3-6 months after mild stroke and transient ischaemic attack: an observational study. BMJ Open 2013;3:e003105.
[31] Swieten JCv, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–7.
[32] Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. Ann Statist 1982;10:1100–20.
[33] And LDF, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. Ann Rev Public Health 1999;20:145–57.
[34] Lee PH. Should we adjust for a confounder if empirical and theoretical criteria yield contradictory results? A simulation study. Sci Rep 2014;4:6085.
[35] Bell CL, Lacroix A, Masaki K, et al. Prestroke factors associated with poststroke mortality and recovery in older women in the Women's Health Initiative. J Am Geriatr Soc 2013;61:1324–30.
[36] Vemmos K, Ntaios G, Spengos K, et al. Association between obesity and mortality after acute first-ever stroke: the obesity-stroke paradox. Stroke 2011;42:30–6.
[37] Dehlendorff C, Andersen KK, Olsen TS. Body mass index and death by stroke: no obesity paradox. JAMA Neurol 2014;71:978–84.
[38] Ryu WS, Lee SH, Kim CK, et al. Body mass index, initial neurological severity and long-term mortality in ischemic stroke. Cerebrovasc Dis 2011;32:170–6.
[39] Kawase S, Kowa H, Suto Y, et al. Association between body mass index and outcome in Japanese ischemic stroke patients. Geriatr Gerontol Int 2016;17:369–74.
[40] Zhao L, Du W, Zhao X, et al. Favorable functional recovery in overweight ischemic stroke survivors: findings from the China National Stroke Registry. J Stroke Cerebrovasc Dis 2014;23:e201–6.
[41] Gomes F, Emery PW, Weekes CE. Mortality and Stroke Recurrence in Obese Stroke Patients: The Obesity Paradox in a London-Based Population. International Stroke Conference (poster presentation); 45 (San Diego, California). 2014
[42] Kim B, Lee S, Ryu W, et al. Paradoxical longevity in obese patients with intracerebral hemorrhage. Neurology 2011;76:567–73.
[43] Clark AL, Fonarow GC, Horwich TB, et al. Survival in systolic heart failure: the obesity paradox revisited. J Cardiac Failure 2011;17:374–80.
[44] Kalantarzadeh K, Abbott KC, Salahudeen AK, et al. Survival advantages of obesity in dialysis patients. Am J Clin Nutr 2005;81:543–54.
[45] Carnethon MR, Rasmussentorvik LJ, Palaniappan L. The obesity paradox in diabetes. Curr Cardiol Rep 2014;16:446.
[46] Tseng C. Obesity paradox: differential effects on cancer and noncancer mortality in patients with type 2 diabetes mellitus. Atherosclerosis 2013;226:186–92.
[47] Brunner AM, Sadrzadeh H, Feng Y, et al. Association between baseline body mass index and overall survival among patients over age 60 with acute myeloid leukemia. Am J Hematol 2013;88:642–4.
[48] Tsang NM, Pai PC, Chuang CC, et al. Overweight and obesity predict better overall survival rates in cancer patients with distant metastases. Cancer Med 2016;5:665–75.
[49] Proietti M, Guiducci E, Cheli P, et al. Is there an obesity paradox for outcomes in atrial fibrillation? a systematic review and meta-analysis of non-vitamin k antagonist oral anticoagulant trials. Stroke 2017;48: 857–66.
[50] Brandt M, Harder K, Walluscheck K, et al. Severe obesity does not adversely affect perioperative mortality and morbidity in coronary artery bypass surgery. Eur J Cardiothorac Surg 2001;19:662–6.
[51] Park JH, Lee J, Ovbiagele B. Association of optimal combination drug treatment with obesity status among recent ischemic stroke patients: results of the Vitamin Intervention for Stroke Prevention (VISP) Trial. J Stroke 2017;19:213–21.
[52] Stapleton RD, Dixon AE, Parsons PE, et al. The association between bmi and plasma cytokine levels in patients with acute lung injury. Chest 2010;138:568–77.
[53] Raimondo D, Tuttolomondo A, Buttà C, et al. Metabolic and anti-inflammatory effects of a home-based programme of aerobic physical exercise. Int J Clin Pract 2013;67:1247–53.
[54] Tuttolomondo A, Maida C, Pinto A. Diabetic foot syndrome as a possible cardiovascular marker in diabetic patients. J Diabetes Res 2015;2015:1–2.
[55] Tuttolomondo A, Maida C, Pinto A. Diabetic foot syndrome: Immune-inflammatory features as possible cardiovascular markers in diabetes. World J Orthop 2015;6:62–76.
[56] Memtsoudis SG, Bombardieri AM, Ma Y, et al. Mortality of patients with respiratory insufficiency and adult respiratory distress syndrome after surgery: the obesity paradox. J Intensive Care Med 2012;27: 306–11.
[57] Strandberg TE, Strandberg AY, Salomaa V, et al. Explaining the obesity paradox: cardiovascular risk, weight change, and mortality during long-term follow-up in men. Eur Heart J 2009;30:1720–7.
[58] Von Haehling S, Horwich TB, Fonarow GC, et al. Tipping the scale heart failure, body mass index, and prognosis. Circulation 2007;116:588–90.
[59] Bruce O, Bath PM, Daniel C, et al. Obesity and recurrent vascular risk after a recent ischemic stroke. Stroke 2011;42:397–402.
[60] Kernan WN, Inzucchi SE, Sawan C, et al. Obesity a stubbornly obvious target for stroke prevention. Stroke 2013;44:278–86.
[61] Whitlock , Lewington G, Sherliker S, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;373:1083–96.
[62] Skolarus LE, Sanchez BN, Levine DA, et al. Association of body mass index and mortality after acute ischemic stroke. Circ Cardiovasc Qual Outcomes 2014;7:64–9.
[63] Connor GS, Tremblay M, Moher D, et al. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. Obes Rev 2007;8:307–26.
[64] Reidpath DD, Cheah CH, Lam FC, et al. Validity of self-measured waist and hip circumferences: results from a community study in Malaysia. Nutr J 2013;12:135–45.
[65] Ng SP, Korda R, Clements M, et al. Validity of self-reported height and weight and derived body mass index in middle-aged and elderly individuals in Australia. Aust New Zealand J Public Health 2011; 35:557–63.
[66] Okorodudu DO, Jumean MF, Montori VM, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. Int J Obes 2010; 34:791–9.

[67] Rodeamontero ER, Eviaviscarra ML, Apolinarjiménez E. Waist-to-height ratio is a better anthropometric index than waist circumference and BMI in predicting metabolic syndrome among obese Mexican adolescents. Int J Endocrinol 2014;2014:195407–195407.

[68] Yamborisut U, Sakamoto N, Wimonpeerapattana W, et al. Waist circumference and body fat distribution indexes as screening tools for the overweight and obesity in Thai preschool children. Obes Res Clin Pract 2010;4:e307–14.

[69] Preston SH, Stokes A. Obesity paradox: conditioning on disease enhances biases in estimating the mortality risks of obesity. Epidemiology 2014;25:454–61.

[70] Sperrin M, Candlish J, Badrick E, et al. Collider bias is only a partial explanation for the obesity paradox. Epidemiology 2016;27:525–30.