Neurotoxicity Research (2019) 36:836–843
https://doi.org/10.1007/s12640-019-00056-4

ORIGINAL ARTICLE

Association of Body Mass Index and Risk of Stroke After Acute Minor Stroke or TIA: a Post Hoc Analysis of a Randomized Controlled Trial

Weiqi Chen[1,2,3,4] • Yuesong Pan[1,2,3,4] • Jing Jing[1,2,3,4] • Xingquan Zhao[1,2,3,4] • Liping Liu[1,2,3,4] • Xia Meng[1,2,3,4] • Yilong Wang[1,2,3,4] • Yi Lin[5,6] • Yongjun Wang[1,2,3,4] • On behalf of the CHANCE Investigators

Received: 12 April 2019 / Accepted: 26 April 2019 / Published online: 24 May 2019

Abstract

The "obesity paradox" was reported in patients with stroke. We aimed to evaluate the pattern and magnitude of association between body mass index (BMI) and prognosis of stroke in patients with minor ischemic stroke or transient ischemic attack (TIA). A total of 5163 patients with available BMI data from the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial were included. Patients were classified into three groups according to their BMI values: normal weight (< 23.9 kg/m^2), overweight (24–27.9 kg/m^2), and obese (≥ 28.0 kg/m^2). The efficacy outcomes included a new stroke (ischemic or hemorrhagic), poor functional outcome defined as modified Rankin scale ≥ 2 points and death from any cause within 90 days. The interaction effects were determined using multivariable Cox or logistic regression models. After 90 days of follow up, there were 513 new strokes. Overweight (BMI 24–27.9 kg/m^2) patients had a higher risk of recurrent strokes than those with normal weight (10.8% vs 8.8%; HR = 1.24, 95% CI 1.02–1.50) after adjusting for the baseline covariates, but no significant association was observed for those who were obese ($P = 0.37$). No significant association was found between being overweight or obese and poor functional outcome or death. For patients with a minor ischemic stroke or TIA, being overweight was associated with an increased risk of recurrent stroke compared to being of normal weight in our study.

Trial registration: URL:http://www.clinicaltrials.gov. Unique identifier: NCT00979589.

Keywords Body mass index · Ischemic stroke · Obesity · Prognosis · Transient ischemic attack

Introduction

Being overweight or obese is associated with progressively increasing risk of ischemic stroke (Bazzano et al. 2010; Strazzullo et al. 2010). Because of this confirmed knowledge in the general population, individuals are advised to strive for a normal weight (Sacco et al. 2006). However, contrary to this recommendation, various studies have shown that patients who are overweight or obese with numerous chronic diseases, including stroke, have lower mortality rates than normal weight or underweight patients (Kim et al. 2012; Olsen et al. 2008; Vemmos et al. 2011). This unexpected association of obesity with improved prognosis after stroke has been termed as the "obesity paradox" and has led to uncertainty about the effects of being overweight or obese (Kernan et al. 2013; Scherbakov et al. 2011; Kernan et al. 2014). Conversely, some other studies have demonstrated that obesity is not associated with a lower risk of death after a stroke (Dehlendorff et al. 2014; Towfighi and Ovbiagele 2009).

Furthermore, most studies have only reported death as an outcome after an ischemic stroke or TIA (Vemmos et al. 2011; Skolarus et al. 2014; Wohlfahrt et al. 2015). Few studies have reported the endpoint of post-stroke disability or stroke

✉ Yi Lin
doctorlinyi78@gmail.com

✉ Yongjun Wang
wangyongjun@ncrcnd.org.cn

1 Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

2 China National Clinical Research Center for Neurological Diseases, Beijing, China

3 Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China

4 Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, Beijing, China

5 Department of Neurology and Institute of Neurology, First Affiliated Hospital, Fujian Medical University, Fujian, China

6 Fujian Key Laboratory of Molecular Neurology, Fujian Medical University, Fuzhou, China

recurrence (Doehner et al. 2013; Andersen and Olsen 2015). Therefore, the relationship between obesity and recurrent strokes has not been well established (Kernan et al. 2014). Moreover, factors associated with stroke recurrence and post-stroke disability in patients with minor stroke or TIA were different from those in patients with ischemic stroke (Ois et al. 2008). It is still unknown whether or not the obesity paradox exists in patients with minor stroke and TIA. Thus, the relationship between being overweight or obese and the risk of recurrent stroke and post-stroke disability in patients with minor stroke or TIA should be further examined. The body mass index (BMI) cutoffs for the Chinese population as recommended by the Obesity Working Group of International Life Science Association of China is as follows: normal weight, overweight, and obesity are defined as < 23.9 kg/m^2, 24–27.9 kg/m^2, and ≥ 28.0 kg/m^2 respectively (Zeng et al. 2014; Zhou 2002; Hsu et al. 2015).

Among patients with minor stroke or TIA, we compared the risk of recurrent stroke and post-stroke disability in those with overweight or obese to those with normal weight.

Materials and Methods

Study Participants

Data were derived from the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial. The CHANCE trial was a randomized, double-blind, controlled trial that enrolled 5170 patients within 24 h after onset of minor stroke (NIH Stroke Scale [NIHSS] ≤ 3) or high-risk TIA (ABCD^2 ≥ 4) from 114 clinical centers in China (Wang et al. 2010, 2013, 2015). Patients without data for weight or height were excluded from our study because they were essential factors for the definition of BMI. The CHANCE trial was registered at clinicaltrials.gov (URL:http://www.clinicaltrials.gov. Unique identifier: NCT00979589). The protocol and data collection of the CHANCE trial were approved by ethics committee of Beijing Tiantan Hospital and all other participating hospitals, in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal proxies.

Demographics and Clinical Characteristics

Baseline demographics and clinical characteristics, including age, gender, history of ischemic stroke, TIA, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, hypertension, diabetes, hypercholesterolemia, smoking status, index event, and NIH stroke scale on admission, time to randomization and antiplatelet therapy were collected through face-to-face interviews by neurologists from clinical centers. Body weight and height were measured by the stroke unit nurses on admission.

Assessment of BMI

BMI was calculated by weight in kilograms divided by the square of the height in meters (kg/m^2). Based on the optimal cut-off of BMI for the Chinese population as recommended by Obesity Working Group of International Life Science Association of China, patients were classified into three groups according to their BMI values: normal weight (< 23.9 kg/m^2), overweight (24–27.9 kg/m^2), and obese ($\geq$ 28.0 kg/m^2) (Zeng et al. 2014; Zhou 2002; Hsu et al. 2015).

Efficacy Outcomes

The efficacy outcomes included having a new stroke (ischemic or hemorrhagic), poor functional outcome defined as modified Rankin Scale (mRS) ≥ 2 points, and death from any cause within 90 days (Wang et al. 2013). Stroke was defined by the presence of sudden new symptomatic neurological deficits on a background of stability or improvement after the presenting event (Rothwell et al. 2007). Secondary efficacy outcomes included composite events (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death) and ischemic strokes (Wang et al. 2013). All the events were evaluated and confirmed by a central adjudication committee that was blinded to the study-group assignments.

Statistical Analysis

We presented categorical variables of baseline characteristics as proportions and continuous variables as medians with interquartile ranges (IQRs). Baseline characteristics among different weight statuses were compared with Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables.

We assessed the interaction effect of weight status by treatment group assignment using weight status × treatment group assignment in multivariable models. Then, we assessed the association between weight status and prognosis of minor stroke or TIA. Adjusted hazards ratios (HRs) and their 95% confidence intervals (CIs) for stroke recurrence were calculated based on the multivariable Cox regression models. Adjusted odds ratios (ORs) and their 95% CIs for poor outcome were calculated based on the multivariable logistic regression models. Both Cox and logistic regressions were analyzed by two models. In the first model, we adjusted only age and gender. In the second model, we included all the potential covariates listed in Table 1. To further assess the influence of age on the association between weight status and outcomes, we performed the analysis by age categories (< 65 years vs. ≥ 65 years) (Suk et al. 2003). We assessed the interaction effect of weight status by age category using weight status × age category in multivariable models. We performed a Cox regression model with restricted cubic splines for BMI (continuous variable) adjusting for covariates to evaluate the pattern and magnitude of associations between BMI and risk of stroke and a logistic regression model with restricted cubic splines for BMI for the endpoint of poor functional outcome. BMI of 24 was treated as the reference and the 5 knots for spline were placed at the 5th, 25th, 50th, 75th, and 95th percentiles of BMI. A two-sided P value < 0.05 was considered to be statistically significant. All analyses were performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics

A total of 5170 patients with minor ischemic stroke or TIA were enrolled in the CHANCE trial. After excluding 7 patients with missing data for weight and height at baseline, 5163 patients were included in the analysis. Among the 5163 patients included, the median age was 62.3 (IQR 54.7–71.2), and 1748 (33.9%) were female.

Among the 5163 patients, the median BMI was 24.5 kg/m^2 (ranging from 15.0 to 37.1). There were 2148 (41.6%), 2351 (45.5%), and 664 (12.9%) patients identified as normal weight, overweight and obese, respectively. Compared to patients with normal weight, obese patients were younger, more likely to be female, had more vascular risk factors (such as

Table 1 Baseline characteristics of the patients by body mass index (BMI) categories

Characteristic	Normal Weight (N = 2148)	Overweight (N = 2351)	Obese (N = 664)	P value
Age (year), median (IQR)	64.1 (56.2–73.2)	61.1 (53.9–70.3)	60.1 (53.6–68.1)	< 0.001
Female, *n* (%)	742(34.5)	719(30.6)	287(43.2)	< 0.001
Weight	61.1 ± 7.5	72.4 ± 6.9	82.5 ± 9.0	< 0.001
BMI	21.9 ± 1.6	25.7 ± 1.1	29.9 ± 1.6	< 0.001
Medical history, *n* (%)				
Ischemic stroke	387 (18.0)	518 (22.0)	123 (18.5)	0.002
TIA	62 (2.9)	86 (3.7)	26 (3.9)	0.25
Myocardial infarction	37 (1.7)	48 (2.0)	11 (1.7)	0.67
Angina	61 (2.8)	92 (3.9)	31 (4.7)	0.04
Congestive heart failure	24 (1.1)	41 (1.7)	14 (2.1)	0.10
Known atrial fibrillation or flutter	77 (3.6)	71 (3.0)	28 (4.2)	0.27
Valvular heart disease	12 (0.6)	2 (0.1)	0 (0.0)	0.003
Hypertension	1287 (59.9)	1599 (68.0)	506 (76.2)	< 0.001
Diabetes	389 (18.1)	532 (22.6)	170 (25.6)	< 0.001
Hypercholesterolemia	167(7.8)	303 (12.9)	102 (15.4)	< 0.001
Smoking status, *n* (%)				0.19
Never smoking	1233 (57.4)	1317 (56.0)	396 (59.6)	
Previous smoker	195 (9.1)	255 (10.9)	64 (9.6)	
Current smoker	720 (33.5)	779 (33.1)	204 (30.7)	
Index event, *n* (%)				0.31
Minor stroke	1566 (72.9)	1690 (71.9)	464 (69.9)	
TIA	582 (27.1)	661 (28.1)	200 (30.1)	
NIHSS score on admission, median (IQR)	2 (0–2)	2 (0–2)	2 (0–2)	0.47
Mean time to randomization (h)	12.2 (6.5–19.5)	11.7 (6.3–19.5)	11.5 (6.3–19.0)	0.19
Time to randomization, *n* (%)				0.35
< 12 h	1043 (48.6)	1187 (50.5)	338 (50.9)	
≥ 12 h	1105 (51.4)	1164 (49.5)	326 (49.1)	
Antiplatelet therapy, *n* (%)				0.02
Aspirin only	1024 (47.7)	1216 (51.7)	341 (51.4)	
Clopidogrel + aspirin	1124 (52.3)	1135 (48.3)	323 (48.6)	

BMI body mass index, *IQR* interquartile range, *NIHSS* National Institutes of Health stroke scale, *TIA* transient ischemic attack angina, hypertension, diabetes and hypercholesterolemia), and less likely to be on dual antiplatelet therapy. Meanwhile, overweight patients were more likely to have a history of ischemic stroke (Table 1).

Association of Weight Status with Outcome

There were 513 (9.9%) new stroke occurrence within 90 days, among which 497 (96.9%) were ischemic strokes and 16 (3.1%) were hemorrhagic strokes. There was no interaction effect of weight status by antiplatelet treatment assignment for the risk of new stroke (P for interaction = 0.67 in the fully adjusted model). Table 2 shows the 90-day risk of stroke after a minor stroke or TIA across categories of weight status. Compared to patients with normal weight, overweight patients had approximately 1.25-fold higher risk of stroke (including ischemic and hemorrhagic stroke) at 90 days after fully adjusting for potential covariates (10.8% vs. 8.8%; adj.HR = 1.24, 95%CI 1.02–1.50), whereas no significant association was observed in those who were obese (10.2% vs. 8.8%; adj.HR = 1.14, 95%CI 0.86–1.51) (Table 2). Similar results were found for the endpoints of composite vascular events and ischemic stroke. No significant association was found between being overweight, obese, and poor functional outcome or death from any cause. There was no interaction effect of age group by weight categories for the risk of stroke or poor outcome (P for interaction = 0.26 and 0.64 in the fully adjusted model, respectively) (Table 3).

Using a multivariable Cox regression model with restricted cubic spline, we found a rotated L-shaped association between BMI and risk of stroke with a threshold of 24 kg/m^2 (Fig. 1). On the other hand, using a multivariable logistic model with restricted cubic spline, we observed a weak U-shaped association between BMI and risk of poor functional outcome at 90-day with a dinar of 24 kg/m^2.

Discussion

The present study showed that being overweight was associated with an increased risk of recurrent strokes compared to being of normal weight. However, obesity was not related to recurrent strokes. Also, being overweight or obese was not related to poor functional outcome after a minor stroke or TIA. In our study, the obesity paradox was not observed in patients with minor stroke or TIA.

Table 2 Outcomes at 90 days for weight categories after minor stroke or TIA

Outcomes	Weight status	Number	Events, *n* (%)	Model 1[c] Adj.HR/OR (95% CI)[e]	*P* value	Model 2[d] Adj. HR/OR (95% CI)[e]	*P* value
Stroke	Normal Weight	2148	190 (8.8)	1		1	
	Overweight	2351	255 (10.8)	1.29 (1.07–1.56)	0.008	1.24 (1.02–1.50)	0.03
	Obese	664	68 (10.2)	1.21 (0.91–1.60)	0.18	1.14 (0.86–1.51)	0.37
Composite events[a]	Normal Weight	2148	191 (8.9)	1		1	
	Overweight	2351	261 (11.1)	1.31 (1.09–1.59)	0.005	1.26 (1.04–1.52)	0.02
	Obese	664	69 (10.4)	1.22 (0.93–1.61)	0.16	1.15 (0.87–1.52)	0.34
Ischemic stroke	Normal Weight	2148	181 (8.4)	1		1	
	Overweight	2351	249 (10.6)	1.32 (1.09–1.60)	0.004	1.27 (1.04–1.54)	0.02
	Obese	664	67 (10.1)	1.25 (0.94–1.66)	0.12	1.17 (0.88–1.56)	0.27
Poor functional outcome[b]	Normal Weight	2132	219 (10.3)	1		1	
	Overweight	2333	261 (11.2)	1.16 (0.96–1.41)	0.12	1.11 (0.91–1.35)	0.31
	Obese	660	71 (10.8)	1.12 (0.84–1.49)	0.45	1.07 (0.80–1.44)	0.65
Death	Normal Weight	2148	9 (0.4)	1		1	
	Overweight	2351	9 (0.4)	1.09 (0.43–2.78)	0.85	1.09 (0.42–2.83)	0.86
	Obese	664	2 (0.3)	0.85 (0.18–3.97)	0.83	0.81 (0.17–3.90)	0.79

CI confidence interval, *HR* hazard ratio, *OR* odds ratio, *TIA* transient ischemic attack

[a] Composite events: stroke, myocardial infarction, or death from cardiovascular causes

[b] Poor functional outcome: modified Rankin Scale 2–6

[c] Model 1: Adjusted for age and gender

[d] Model 2: Adjusted for age, gender, history of ischemic stroke, TIA, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, hypertension, diabetes, hypercholesterolemia, smoking status, index event and NIH stroke scale on admission, time to randomization and antiplatelet therapy

[e] HR calculated for stroke recurrence and death, OR calculated for poor functional outcome

Table 3 Outcomes at 90 days for weight categories after minor stroke or TIA by age categories

Outcomes	Weight status	Age < 65 years				Age ≥ 65 years				*P* for interaction
		N	Events, *n* (%)	Adj. HR/OR (95% CI)[b,c]	*P* value	*N*	Events, *n* (%)	Adj. HR/OR (95% CI)[b,c]	*P* value	
Stroke	Normal Weight	1130	95 (8.4)	1		1018	95 (9.3)	1		0.26
	Overweight	1460	135 (9.2)	1.04 (0.80–1.36)	0.75	891	120 (13.5)	1.45 (1.11–1.91)	0.008	
	Obese	438	44 (10.0)	1.11 (0.77–1.59)	0.58	226	24 (10.6)	1.05 (0.66–1.65)	0.85	
Poor functional outcome[a]	Normal Weight	1120	103 (9.2)	1		1012	116 (11.5)	1		0.64
	Overweight	1447	137 (9.5)	0.95 (0.72–1.25)	0.70	886	124 (14.0)	1.26 (0.95–1.67)	0.11	
	Obese	436	43 (9.9)	0.98 (0.67–1.44)	0.91	224	28 (12.5)	1.04 (0.66–1.65)	0.86	

CI confidence interval, *HR* hazard ratio, *OR* odds ratio, *TIA* transient ischemic attack

[a] Poor functional outcome: modified Rankin Scale 2–6

[b] Adjusted for gender, history of ischemic stroke, TIA, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, hypertension, diabetes, hypercholesterolemia, smoking status, index event and NIH stroke scale on admission, time to randomization and antiplatelet therapy

[c] HR calculated for stroke recurrence and death, OR calculated for poor functional outcome

Though various studies indicate a survival benefit of obese individuals, the impact of BMI on recurrent stroke was less well established, especially for minor stroke or TIA. Reports of obesity paradox might lead to uncertainty about secondary prevention in excess body weight patients with stroke. Our study did not show the obesity paradox. Higher BMI might be associated with stroke recurrence in patients with minor stroke or TIA. Although not statistically significant, the risk of stroke recurrence in patients with obesity was higher than those with normal weight, which may be caused by the small sample size in the obese group ($n = 664$). Data from the African American Antiplatelet Stroke Prevention Study also showed an association between being overweight and an increased risk of stroke recurrence (Ruland et al. 2005). However, a previous study found that obese patients had lower overall vascular risk than those with normal weight, but not related to recurrent stroke risk in patients with a recent ischemic stroke or TIA (Ovbiagele et al. 2011). Another study showed the obesity paradox in that overweight and obese patients with stroke or TIA had a lower risk of recurrent stroke than patients with BMI ≤ 25 kg/m^2 (Doehner et al. 2013). Furthermore, we failed to observe an influence of age on the association of weight status with prognosis of stroke.

Although not statistically significant, our study demonstrated a slight trend that being overweight or obese was related to poor functional outcome for patients with a minor stroke or TIA. This could potentially be explained by the small sample size and mild disabilities of patients in our study. Furthermore, our study revealed a weak U-shaped relationship between obesity and the risk of poor functional outcome. The U-shaped curve showed that the lowest risk of poor functional outcome was associated with a BMI of 24 kg/m^2 which was boundary between normal weight and overweight. A BMI of 24 kg/m^2 was found to have the best sensitivity and specificity for risk-factor identification and was recommended as the cut-off point for the overweight range for the Chinese population (Zhou 2002; Hsu et al. 2015). Meanwhile, a BMI of 28 kg/ m^2 was found to identify risk factors with specificity of approximately 90% and was recommended as the cut-off point for the obese category (Zhou 2002; Hsu et al. 2015). Thus, in this post-hoc analysis, we applied the recommended definition of overweight and obesity for Chinese patients for analysis.

The secondary stroke prevention guidelines mentioned that the usefulness of weight loss among obese patients with a recent TIA or ischemic stroke was uncertain (Kernan et al. 2014). In the present study, obesity was a risk factor for stroke recurrence rather than a protective factor as described by the obesity paradox. Minor strokes and TIAs account for approximately 65% of all acute ischemic cerebrovascular events (von Weitzel-Mudersbach et al. 2013) and lead to 10% to 15% increase in the risk of stroke occurrence within 90 days (Giles and Rothwell 2007). Even with medical intervention, minor stroke and TIA still lead to a high risk of recurrence, which could raise the disability rate (Giles and Rothwell 2007; Coull et al. 2004). Our study added the evidence that being overweight was associated with an increased risk of a new stroke in patients with minor stroke and TIA. Thus, it may be significant to provide recommendation to overweight and obese patients with minor strokes or TIAs to strive to reach a

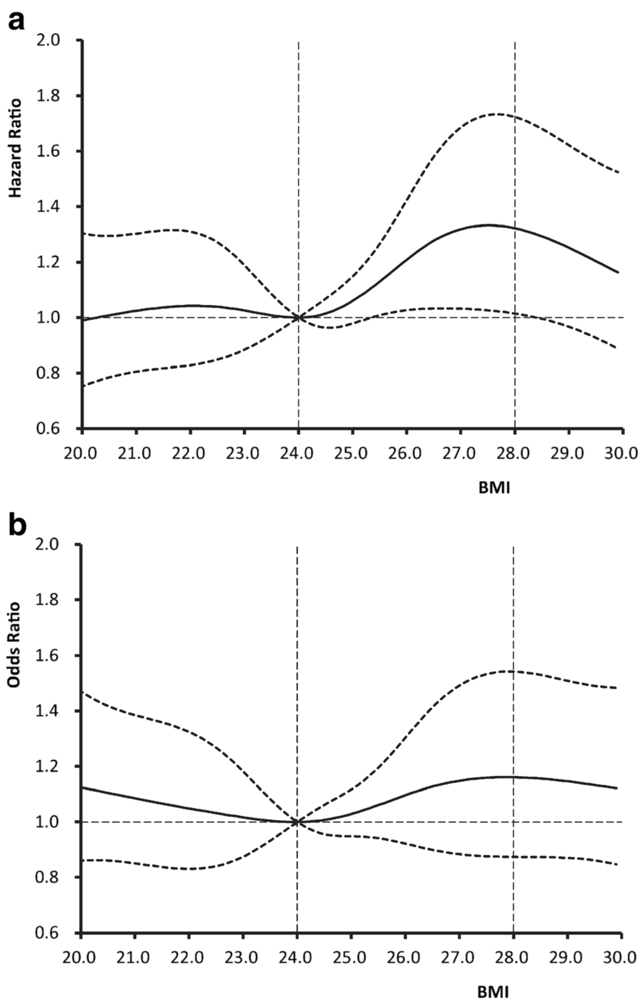

Fig. 1 Adjusted hazard ratios for new stroke (**a**) and odds ratios for poor functional outcome (**b**) according to body mass index (BMI) at baseline. The solid line indicates estimated hazard ratio or odds ratios, and the dashed lines indicate the 95% confidence interval bands. Reference was BMI of 24 kg/m^2. Data were fitted using a Cox or logistic regression model of restricted cubic spline with 5 knots (the 5th, 25th, 50th, 75th, 95th percentiles) for BMI adjusting for potential covariates. The lowest 5% and highest 5% of participants were not shown in the figures for small sample sizes

normal weight. The association of BMI and stroke recurrence has not been studied before, and our study indicated that this association might be very different from that in patients with ischemic stroke. Further prospective cohort studies are needed to evaluate the relationship between BMI and stroke recurrence in patients with minor stroke or TIA.

Our study has some limitations. First, only 20 patients (0.4%) died in our study; thus, we cannot assess the relationship between the obesity and mortality. Some (Vemmos et al. 2011; Ovbiagele et al. 2011) but not all previous studies (Dehlendorff et al. 2014; Towfighi and Ovbiagele 2009; Skolarus et al. 2014) reported the obesity paradox in patients with stroke using death as an outcome measurement. Second, the characteristics of minor stroke and TIA patients enrolled in this study were different from those in typical minor stroke or TIA population-based cohorts. Most of the minor stroke patients recruited in this study had non-cardiogenic embolism and TIA patients had a high risk of having a stroke (ABCD^2 scores ≥ 4), which may have resulted in a high recurrence rate. Large-scale population-based cohorts testing the association of being overweight or obese with recurrent stroke and poor functional outcome are needed to confirm our results. Third, only Chinese patients were enrolled in our study, and further evaluation of patients in other races who are overweight or obese with minor stroke and TIA might also be required. Fourth, we did not collect information on waist circumference or hip circumference in the CHANCE study. Waist to hip ratio or waist circumference in addition to the BMI might be better correlated to the findings than BMI alone. Fifth, obese people tend to have other co-morbidity and different baseline health. Some potential variance which was related to the obesity was not analyzed because the data were not collected in the CHANCE study, which might cause bias. Finally, the data of etiology classification for patients in the CHANCE trial was not available and we could not analyze the association between being overweight or obese and stroke subtypes, which may be significant for mechanistic explanations. Previous studies have shown that the obesity paradox could be related to the etiology classification of ischemic stroke (Ovbiagele et al. 2011).

Conclusions

In conclusion, for patients with a minor ischemic stroke or TIA in our study, being overweight was associated with an increased risk of recurrent stroke compared to being of normal weight in our study. Further prospective cohort studies with larger-scale sample size are needed to evaluate the relationship between BMI and stroke recurrence in patients with minor stroke or TIA.

Acknowledgements We appreciated all the patients, relevant clinicians, imaging, and laboratory technicians who participated in the study and many individuals not specifically mentioned in the paper who have supported the study.

Funding Information This study was supported by the National Natural Science Foundation of China(81870929), grants from National Key Technology Research and Development Program of the Ministry of Science and Technology of the People's Republic of China (2015BAI12B04 and 2015BAI12B02), a grant from Beijing Municipal Science and Technology Commission (D151100002015001), a grant from Beijing Institute for Brain Disorders (1152130306), Joint Funds of Science and Technology Innovation of Fujian Province (2017Y9086), a grant from Medical Innovation Project for Research Talents of Fujian Province (2018-CX-25), and a grant from Science and Technology Major Project of Fujian Province (2017YZ0001-1).

Compliance with Ethical Standards

The protocol and data collection of the CHANCE trial were approved by ethics committee of Beijing Tiantan Hospital and all other participating hospitals, in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal proxies.

Conflict of Interest The authors declare that there are no conflicts of interest.

Abbreviations BMI, Body mass index; CHANCE, Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events; CI, Confidence intervals; IQR, Interquartile range; mRS, Modified Rankin Scale; TIA, Transient ischemic attack; NIHSS, National Institutes of Health stroke scale

References

Andersen KK, Olsen TS (2015) The obesity paradox in stroke: lower mortality and lower risk of readmission for recurrent stroke in obese stroke patients. Int J Stroke 10(1):99–104

Bazzano LA, Gu D, Whelton MR, Wu X, Chen CS, Duan X, Chen J, Chen JC, He J (2010) Body mass index and risk of stroke among Chinese men and women. Ann Neurol 67(1):11–20. https://doi.org/10.1002/ana.21950

Coull AJ, Lovett JK, Rothwell PM, Oxford Vascular S (2004) Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 328(7435):326. https://doi.org/10.1136/bmj.37991.635266.44

Dehlendorff C, Andersen KK, Olsen TS (2014) Body mass index and death by stroke: no obesity paradox. JAMA Neurol 71(8):978–984. https://doi.org/10.1001/jamaneurol.2014.1017

Doehner W, Schenkel J, Anker SD, Springer J, Audebert HJ (2013) 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 34(4):268–277. https://doi.org/10.1093/eurheartj/ehs340

Giles MF, Rothwell PM (2007) Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 6(12):1063–1072. https://doi.org/10.1016/S1474-4422(07)70274-0

Hsu WC, Araneta MR, Kanaya AM, Chiang JL, Fujimoto W (2015) BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. Diabetes Care 38(1):150–158. https://doi.org/10.2337/dc14-2391

Kernan WN, Inzucchi SE, Sawan C, Macko RF, Furie KL (2013) Obesity: a stubbornly obvious target for stroke prevention. Stroke 44(1):278–286. https://doi.org/10.1161/STROKEAHA.111.639922

Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease (2014) 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 45(7):2160–2236. https://doi.org/10.1161/STR.0000000000000024

Kim BJ, Lee SH, Jung KH, Yu KH, Lee BC, Roh JK, For Korean Stroke Registry investigators (2012) Dynamics of obesity paradox after stroke, related to time from onset, age, and causes of death. Neurology 79(9):856–863. https://doi.org/10.1212/WNL.0b013e318266fad1

Ois A, Gomis M, Rodriguez-Campello A, Cuadrado-Godia E, Jimenez-Conde J, Pont-Sunyer C et al (2008) Factors associated with a high risk of recurrence in patients with transient ischemic attack or minor stroke. Stroke 39(6):1717–1721. https://doi.org/10.1161/STROKEAHA.107.505438

Olsen TS, Dehlendorff C, Petersen HG, Andersen KK (2008) Body mass index and poststroke mortality. Neuroepidemiology 30(2):93–100. https://doi.org/10.1159/000118945

Ovbiagele B, Bath PM, Cotton D, Vinisko R, Diener HC (2011) Obesity and recurrent vascular risk after a recent ischemic stroke. Stroke 42(12):3397–3402. https://doi.org/10.1161/STROKEAHA.111.624957

Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN et al (2007) Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet 370(9596):1432–1442. https://doi.org/10.1016/S0140-6736(07)61448-2

Ruland S, Hung E, Richardson D, Misra S, Gorelick PB (2005) African American antiplatelet stroke prevention study I. impact of obesity and the metabolic syndrome on risk factors in African American stroke survivors: a report from the AAASPS. Arch Neurol 62(3):386–390. https://doi.org/10.1001/archneur.62.3.386

Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K et al (2006) Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 37(2):577–617. https://doi.org/10.1161/01.STR.0000199147.30016.74

Scherbakov N, Dirnagl U, Doehner W (2011) Body weight after stroke: lessons from the obesity paradox. Stroke 42(12):3646–3650. https://doi.org/10.1161/STROKEAHA.111.619163

Skolarus LE, Sanchez BN, Levine DA, Baek J, Kerber KA, Morgenstern LB, Smith MA, Lisabeth LD (2014) Association of body mass index and mortality after acute ischemic stroke. Circ Cardiovasc Qual Outcomes 7(1):64–69. https://doi.org/10.1161/CIRCOUTCOMES.113.000129

Strazzullo P, D'Elia L, Cairella G, Garbagnati F, Cappuccio FP, Scalfi L (2010) Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. Stroke 41(5):e418–e426. https://doi.org/10.1161/STROKEAHA.109.576967

Suk SH, Sacco RL, Boden-Albala B, Cheun JF, Pittman JG, Elkind MS, Paik MC, Northern Manhattan Stroke Study (2003) Abdominal obesity and risk of ischemic stroke: the northern Manhattan stroke study. Stroke 34(7):1586–1592. https://doi.org/10.1161/01.STR.0000075294.98582.2F

Towfighi A, Ovbiagele B (2009) The impact of body mass index on mortality after stroke. Stroke 40(8):2704–2708. https://doi.org/10.1161/STROKEAHA.109.550228

Vemmos K, Ntaios G, Spengos K, Savvari P, Vemmou A, Pappa T, Manios E, Georgiopoulos G, Alevizaki M (2011) Association between obesity and mortality after acute first-ever stroke: the obesity-stroke paradox. Stroke 42(1):30–36. https://doi.org/10.1161/STROKEAHA.110.593434

von Weitzel-Mudersbach P, Andersen G, Hundborg HH, Johnsen SP (2013) Transient ischemic attack and minor stroke are the most common manifestations of acute cerebrovascular disease: a prospective, population-based study–the Aarhus TIA study. Neuroepidemiology 40(1):50–55. https://doi.org/10.1159/000341696

Wang Y, Johnston SC, Investigators C (2010) Rationale and design of a randomized, double-blind trial comparing the effects of a 3-month clopidogrel-aspirin regimen versus aspirin alone for the treatment of high-risk patients with acute nondisabling cerebrovascular event. Am Heart J 160(3):380–6 e1. https://doi.org/10.1016/j.ahj.2010.05.017

Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, Jia J, Dong Q, Xu A, Zeng J, Li Y, Wang Z, Xia H, Johnston SC, CHANCE Investigators (2013) Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 369(1):11–19. https://doi.org/10.1056/NEJMoa1215340

Wang Y, Pan Y, Zhao X, Li H, Wang D, Johnston SC, Liu L, Meng X, Wang A, Wang C, Wang Y, CHANCE Investigators (2015) Clopidogrel with aspirin in acute minor stroke or transient ischemic attack (CHANCE) trial: one-year outcomes. Circulation 132(1):40–46. https://doi.org/10.1161/CIRCULATIONAHA.114.014791

Wohlfahrt P, Lopez-Jimenez F, Krajcoviechova A, Jozifova M, Mayer O, Vanek J, Filipovsky J, Llano EM, Cifkova R (2015) The obesity paradox and survivors of ischemic stroke. J Stroke Cerebrovasc Dis 24(6):1443–1450. https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.03.008

Zeng Q, He Y, Dong S, Zhao X, Chen Z, Song Z, Chang G, Yang F, Wang Y (2014) Optimal cut-off values of BMI, waist circumference and waist:height ratio for defining obesity in Chinese adults. Br J Nutr 112(10):1735–1744. https://doi.org/10.1017/S0007114514002657

Zhou BF (2002) Cooperative Meta-Analysis Group of the Working Group on Obesity in C. 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 15(1):83–96