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ORIGINAL ARTICLE

Higher body mass index associated with smaller frontal cortical volumes in older adult patients with bipolar disorder

Pao-Huan Chen[a,b,c], **Jung-Lung Hsu**[d], **Kuo-Hsuan Chung**[a,b,c], **Shou-Hung Huang**[a,b,c], **Yu-Jui Huang**[a,b], **Shang-Ying Tsai**[a,b,c,*]

[a] *Department of Psychiatry, Taipei Medical University Hospital, Taipei, Taiwan*
[b] *Psychiatric Research Center, Taipei Medical University Hospital, Taipei, Taiwan*
[c] *Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[d] *Department of Neurology, Chang Gung Memorial Hospital Linkou Medical Center and College of Medicine, Chang Gung University, Taoyuan, Taiwan*

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Abstract
Background and objectives: Patients with bipolar disorder (BD) tend to have accelerated decline in executive function during the aging. Thus far, only few studies have examined the effect of obesity on frontal cortical volumes in young patients with BD. Herein we aimed to ascertain the association between body mass index (BMI) and frontal cortical volumes in older adult patients with BD.
Methods: We recruited outpatients who were diagnosed as bipolar I disorder (BD-I) and aged over 50 years to undergo volumetric magnetic resonance imaging and anthropometric measurement. Clinical data were obtained through interview and chart review.
Results: A total of 42 patients (mean age, 59.5 ± 7.9 years) with BD-I were recruited in this study. Compared with normal BMI group, overweight/obese patients (59.5%, n = 25) had significantly smaller volumes of the bilateral prefrontal cortex and right orbitofrontal cortex. After adjusting cardiometabolic variables, higher BMI and age were significantly associated with smaller volumes of the left prefrontal cortex and bilateral orbitofrontal cortex, accounting for 29.8% (left prefrontal cortex), 33.1% (left orbitofrontal cortex), and 42.0% (right orbitofrontal cortex) of the variance. BMI alone was negatively associated with the volumes of the right prefrontal and right medial frontal cortexes, accounting for 25.7% and 14.7% of the variance, respectively.

* Corresponding author at: Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, #252 Wu-Hsing Street, Taipei, 110, Taipei, Taiwan.
E-mail address: tmcpsyts@tmu.edu.tw (S.-Y. Tsai).

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Conclusions: Higher BMI was associated with smaller cortical volumes across individual frontal regions in older patients with BD independent of cardiometabolic morbidity. Future research is necessary to elucidate the mechanisms underlying the association between BMI and frontal cortical volumes in older patients with BD.

Introduction

Bipolar disorder (BD) is a serious mental illness that typically first manifests in adolescence and young adulthood. In addition to burden caused by mood instability, patients with BD frequently experience cognitive impairment and functional decline as the illness progresses.[1,2,3,4,5] Recently, studies have revealed that compared with the general population, older patients with BD tend to have accelerated age-related decline in the subdomain of executive function, including mental flexibility and processing speed.[3,6,7] Although initial evidence suggests that the microstructural integrity of white matter is more sensitive to the age effect in patients with BD,[6] brain aging and its underlying neurobiological mechanisms are relatively understudied in individuals with BD. Compared with adolescents or young adults with early-stage BD, older BD patients with typical-onset age are more likely to have a longer duration of illness,[8] more exposure to concomitant medications,[9] and higher burden of medical comorbidity.[10,11] All these factors can lead to a more rapid course of neuroprogression in older patients with BD.[12]

Among the medical morbidities, obesity is highly prevalent in patients with BD across the lifespan.[11,13,14,15] In addition to the associated risks of cardiovascular morbidity and mortality,[16] a recent meta-analysis has suggested that in patients with BD, obesity contributes to the impairment of cognitive function, particularly in the subdomain of executive function.[17] Moreover, neuroimaging studies have shown that elevated body mass index (BMI) is associated with reduced volumes of the frontal and temporal cortexes in adolescents and younger adults with BD.[18,19,20,21] The putative mechanisms for this accelerated neuroprogression in BD patients with obesity can be attributed to the increased risk of cardiometabolic diseases,[13,16] elevated levels of inflammatory cytokines and oxidative stress,[22,23,24] and reduced levels of neurotrophic factors.[22,25] Previously, we have found that left hippocampal volumes were negatively associated with BMI in older adults with BD.[26] The findings suggest that obesity is linked to neuroprogression of the hippocampus among older patients with BD. Given the growing evidence that older patients with BD tend to have accelerated age-related decline in the subdomain of executive function,[6,7] an investigation of the association between obesity and frontal cortical volumes of aging patients with BD is highly warranted. Nevertheless, studies on this topic still remain limited in the literature.

In this study, we aimed to ascertain the effect of BMI on the cortical volumes of individual frontal regions in older adults with BD. We hypothesized that higher BMI and age are associated with smaller cortical volumes across the individual frontal regions in older patients with BD. With the considerations that the cardiometabolic burden can be increased in this particular group of patients[27,28,29,30,31,32] and potentially contributes to smaller regional brain volumes,[33,34] we also collected cardiometabolic variables to assess the effect of cardiometabolic diseases on frontal cortical volumes.

Methods

Participants

We recruited participants from the outpatient department of Taipei Medical University Hospital (TMUH) if they met the following inclusion criteria: (1) age over 50 years, (2) a final diagnosis of bipolar I disorder (BD-I) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and (3) at least one psychiatric admission to TMUH. The exclusion criteria were as follows: (1) reported history of stroke or head injury, (2) active substance abuse, (3) mental disorder associated with a general medical condition, (4) any type of dementia, or (5) inability to undergo magnetic resonance imaging (MRI). To confirm the psychiatric diagnosis, each participant was interviewed by two board-certified psychiatrists involved in this study by using the Chinese version of the Structured Clinical Interview for DSM-IV.

Informed consent and Institutional Review Board approval

The Taipei Medical University–Joint Institutional Review Board approved the research protocol. Appropriate procedures were followed in accordance with ethical and legal standards. All participants provided written informed consent before participation.

Procedures

After enrollment into the study, each participant underwent measurement of blood pressure, body weight, and body height. In addition, sociodemographic and clinical data were obtained by interview and chart review. The cut-off point for obesity used in this study was a BMI over 27 kg/m^2 and for overweight a BMI between 24 and 27 kg/m^2.[35] Cardiovascular diseases included ischemic heart disease and hypertension, which are the principle cardiovascular morbidity in patients with BD.[27,30] Participants who had serum fasting glucose

levels above 126 mg/dL or received treatment for diabetes mellitus were identified as having diabetes mellitus. The data extracted from the medical records were rechecked by two psychiatrists to minimize individual errors.

Brain images from each participant were obtained using the 1.5-T MR scanner (Signa Contour; GE-Yokogawa Medical Systems, Tokyo, Japan) with three pulse sequences: (1) 124 contiguous, 1.2-mm-thick axial planes of three-dimensional T1-weighted images (spoiled gradient recalled acquisition in a steady state: repetition time [TR], 40 ms; echo time [TE], 7 ms; flip angle [FA], 90°; voxel size, 0.86 mm × 0.86 mm × 1.2 mm); (2) 58 contiguous, 3-mm-thick axial planes of proton density (PD) images (spin echo [SE]: TR, 2860 ms; TE, 15 ms; voxel size, 0.86 mm × 0.86 mm × 3 mm); and (3) 58 contiguous, 3-mm-thick axial planes of T2-weighted images (SE: TR, 2860 ms; TE, 120 ms; voxel size, 0.86 mm × 0.86 mm × 3 mm). Before computational procedures, MR images were converted into the ANALYZE format using MRIcro software (www.mccauslandcenter.sc.edu/CRNL/). Image analysis was performed using the FMRIB software library (FSL 3.3). The method of image segmentation was based on a hidden Markov random field model and an associated expectation-maximization algorithm. After the segmentation procedure, the brain tissue was classified into different tissue types (e.g., gray matter and white matter) while correcting for spatial intensity variations (i.e., bias field). The individually segmented gray matter mask was automated and labeled into 116 cortical regions. The volume of each region was calculated using the Individual Brain Atlases using the Statistic Parametric Mapping Software toolbox. For interindividual comparison of the different brain regions, each brain region was divided by the individual's total intracranial volume to get the volume in percentage. Previous studies have successfully used this protocol for image collection and analyses.[26,36,37]

The anatomical region of the prefrontal lobe was defined as the dorsolateral part of the superior frontal gyrus, middle frontal gyrus, opercular part of the inferior frontal gyrus, and triangular part of the inferior frontal gyrus.[38] The anatomical region of the orbitofrontal lobe was defined as the orbital part of the superior frontal gyrus, orbital part of the middle frontal gyrus, and orbital part of the inferior frontal gyrus, gyrus rectus, and olfactory lobe. The anatomical region of the medial frontal lobe included the medial part of the superior frontal gyrus, supplementary motor area, and paracentral lobule.

The risk of stroke is elevated in patients with BD.[28,32] Although we excluded those participants with a reported history of stroke, BD patients recruited in this study could still potentially have silent stroke. In the present study, silent stroke was defined as the presence of cerebral infarct on brain MRI of patient without any reported history of stroke. The details of methodology to define the cerebral infarct on MRI have been previously published.[32]

Statistical analysis

For categorical variables, two-group comparisons were performed using the chi-square test with Yates' correction or Fisher's exact test. For continuous variables, two-group comparisons were performed using the independent sample *t* tests. The Pearson correlation was determined to examine the relationship between the frontal cortical volumes of interest and clinical characteristics. Given the exploratory nature of this study, the results of univariate analyses are presented without Bonferroni corrections. The potential variables with an association with each specific region of frontal cortex in the univariate analyses ($P < 0.05$) were selected for entry into the multiple linear regression models. All data analyses were performed using SAS 9.4 software (SAS, Cary, NC, USA). *P* values <0.05 were considered statistically significant.

Table 1 Demographic and clinical characteristics of 42 older patients with bipolar disorder.

Continuous variables	Mean	SD
Age, years	59.5	7.9
Education, years	10.6	4.1
Age at onset of BD, years	33.2	13.7
Duration of illness, years	26.7	13.6
Lifetime mood episodes	11.3	11.3
Lifetime lithium use, years	5.6	6.4
Lifetime valproic acid use, years	4.7	5.9
Lifetime antipsychotic use, years	8.0	9.1
YMRS scores	1.6	2.5
HAMD scores	1.0	2.4
MMSE scores	26.5	4.0
Body mass index, kg/m^2	26.5	5.2
Systolic blood pressure, mmHg	135.5	83.8
Diastolic blood pressure, mmHg	87.2	12.3

Categorical variables	N	%
Male	13	31.0
Marriage	25	59.5
Living with family	36	85.7
Late-onset BD	14	33.3

Abbreviations: BD = bipolar disorder; HAMD = Hamilton Depression Rating Scale; MMSE = Mini–Mental State Examination; YMRS = Young Mania Rating Scale.

Results

In this study, a total of 42 patients (mean age, 59.5 ± 7.9 years) with BD-I were recruited (Table 1). The mean age of disease onset was 33.2 ± 13.7 years. Fourteen (33.3%) of the patients had late-onset BD, which is defined as disease onset at an age cut-off of 40 years as proposed by the International Society for Bipolar Disorders Task Force.[12]

The brain volumes in different cardiometabolic diseases are shown in Table 2. Compared with patients without overweight or obesity, those with overweight or obesity had significantly smaller mean volumes of total gray matter, bilateral prefrontal cortex, and right orbitofrontal cortex. In addition, compared with patients without diabetes mellitus, those with diabetes mellitus had significantly smaller mean volumes of the right prefrontal cortex and right medial frontal cortex. Moreover, compared with patients without cardiovascular diseases, those with cardiovascular diseases had significantly smaller mean volumes of total gray mat-

Table 2 Brain volumes between obesity and cardiometabolic diseases in 42 older patients with bipolar disorder.

Clinical variables			Total gray matter (%)			Total white matter (%)			Prefrontal cortex, left (%)			Prefrontal cortex, right (%)		
		N	Mean	t	*P*	Mean	t	*P*	Mean	t	*P*	Mean	t	*P*
Overweight/Obesity	No	17	44.44	−2.575	0.014*	28.45	−0.438	0.664	1.97	−2.389	0.022*	1.86	−2.734	0.009**
	Yes	25	40.80			28.07			1.68			1.56		
Diabetes mellitus	No	29	43.26	−1.960	0.057	28.14	0.309	0.759	1.88	−1.920	0.062	1.76	−2.253	0.030*
	Yes	13	40.24			28.42			1.62			1.50		
Cardiovascular disease	No	20	43.90	−2.180	0.035*	28.27	−0.080	0.937	1.94	−2.104	0.042*	1.80	−1.971	0.056
	Yes	22	40.80			28.20			1.68			1.58		
Silent stroke	No	26	42.17	0.241	0.811	28.26	−0.076	0.939	1.80	0.097	0.923	1.68	0.095	0.925
	Yes	16	42.55			28.19			1.81			1.69		

Clinical variables			Orbitofrontal cortex, left (%)			Orbitofrontal cortex, right (%)			Medial frontal cortex, left (%)			Medial frontal cortex, right (%)		
		N	Mean	t	*P*	Mean	t	*P*	Mean	t	*P*	Mean	t	*P*
Overweight/Obesity	No	17	1.02	−1.797	0.080	1.00	−2.529	0.015*	0.70	−0.760	0.451	0.76	−1.692	0.098
	Yes	25	0.92			0.87			0.67			0.69		
Diabetes mellitus	No	29	0.99	−1.412	0.166	0.95	−1.515	0.138	0.70	−0.991	0.332	0.74	−2.043	0.048*
	Yes	13	0.90			0.86			0.65			0.66		
Cardiovascular disease	No	20	1.02	−2.158	0.037*	0.98	−1.964	0.057	0.74	−2.582	0.014*	0.75	−1.596	0.118
	Yes	22	0.91			0.87			0.64			0.69		
Silent stroke	No	26	0.95	0.337	0.738	0.93	−0.094	0.926	0.68	0.614	0.543	0.70	1.108	0.277
	Yes	16	0.97			0.92			0.70			0.75		

* $P < 0.05$.
** $P < 0.01$.

ter as well as the left prefrontal, orbitofrontal, and medial frontal cortexes.

Table 3 shows the correlations between the brain volumes of interest and clinical characteristics. Significantly, the volume of total gray matter was negatively correlated with age. The volume of total white matter was positively correlated with the duration of bipolar disorder illness and the lifetime duration of lithium use. Regarding the individual brain regions of interest, the volumes of the bilateral prefrontal, orbitofrontal, and medial frontal cortexes were negatively correlated with BMI and systolic blood pressure. In addition, the volumes of the left prefrontal cortex and bilateral orbitofrontal cortex were inversely correlated with age. Furthermore, the volume of the left orbitofrontal cortex was negatively correlated with the duration of bipolar disorder illness.

To investigate the simultaneous effect of several potential factors on the brain volumes of interest, multiple linear regression analyses were separately performed using variables with statistical significance ($P < 0.05$) in the univariate analyses for each specific region of frontal cortex (Tables 2 and 3). Significantly, higher BMI alone was negatively associated with the volumes of the right prefrontal cortex and right medial frontal cortex, accounting for 25.7% and 14.7% of the variance, respectively (Table 4). In addition, higher BMI and age were significantly associated with smaller volumes of the left prefrontal cortex and bilateral orbitofrontal cortex, accounting for 29.8% (left prefrontal cortex), 33.1% (left orbitofrontal cortex), and 42.0% (right orbitofrontal cortex) of the variance.

Discussion

To the best of our knowledge, this is the first study to investigate the association between BMI and frontal cortical volumes in older patients with BD. We found that higher BMI had a significant association with smaller cortical volumes across the individual frontal regions among older patients with BD. Specifically, after controlling for cardiometabolic variables, higher BMI and age were significantly associated with smaller volumes of the left prefrontal cortex and bilateral orbitofrontal cortex. In addition, BMI alone was negatively associated with the volumes of the right prefrontal and right medial frontal cortexes. Together with research findings in patients with early-stage BD,[18,19,20,21] our present findings suggest that obesity affects the brain health of patients with BD across their lifespan.

Numerous studies across Western and non-Western countries have shown that patients with BD are at increased risks of cardiovascular disease, hypertension, and diabetes mellitus.[27,28,29,30,31,32] Additionally, evidence suggests that these cardiometabolic diseases negatively affect brain volumes.[33,34] In our multivariate analyses, cardiometabolic diseases and blood pressure were not significantly associated with smaller cortical volumes across the individual frontal regions, except for the left medial frontal cortex. One of the possible reasons may be due to the characteristics of our study sample, in that fewer patients had late-onset BD and stroke lesions in our present study as compared to patients in other previous reports.[12,28,39] Therefore, our major finding of the inverse association between BMI and frontal cortical volumes was less confounded by the effects of cardiometabolic morbidities. Besides, obesity-derived neuroinflammation has been shown to affect brain structures.[40] In addition, growing evidence has indicated that neuroinflammation plays a role in the neuroprogression of BD.[22,23,24] To elucidate the mechanisms underlying the negative association between BMI and frontal cortical volumes in older patients with BD, further studies also need to include inflammatory markers in the analyses.

There was a discrepancy between the results of previous studies on early-stage BD and our present findings regarding older-age BD. In the present study, we found that higher BMI was associated with smaller cortical volumes across several frontal regions among older patients with BD. However, the negative association between BMI and frontal cortical volumes was not consistently observed in some previous studies in young adults with first-episode mania.[18,19] The reasons for the discrepancy are unknown. Recently, older patients with BD were found to have an accelerated age-related decline in executive function.[6,7] In addition, neuroimaging evidence suggests that the brains of patients with BD are more sensitive to the age effect.[6] In this study, we found that higher BMI and age were significantly associated with smaller volumes of the left prefrontal cortex and bilateral orbitofrontal cortex. Taken together, these findings may suggest that the frontal lobes of patients with older-age BD are more vulnerable to the age effect during neuroprogression.

In our multivariate analyses, we found that BMI was the only factor negatively associated with the volumes of the right prefrontal cortex and right medial frontal cortex. Recently, a 42-year longitudinal study has found that compared with those with a normal BMI trajectory, older adults (mean age: 62 years) with obesity trajectory had a significantly thinner frontal cortex in the right hemisphere after adjustment for age, cardiovascular risk factors, and inflammatory markers.[41] The finding for left frontal hemisphere did not reach significance. Our findings are therefore in line with those of previous studies suggesting that obesity may exert a stronger detrimental effect on the right frontal lobe in aging adults.

We did not find a significant association between BMI and total white matter volume in our patients with BD. Interestingly, our analyses showed a positive association between total white matter volume and lifetime duration of lithium use. The findings are consistent with those in the literature, suggesting that lithium treatment can protect against white matter volume reduction in patients with mania over time[42] and promote axial connectivity.[43,44] The early work has shown that neuroinflammation due to aging, obesity, and BD pathophysiology may play a role in neuroprogression in BD.[26] Additionally, laboratory studies have shown that lithium can suppress microglial activation and attenuate the overexpression of pro-inflammatory cytokines.[45] Altogether, the anti-inflammatory action of lithium may provide neuroprotection against the detrimental effect of obesity on the brain of BD patients.

Noticeably, emerging evidence from prospective interventional studies has shown that the reduction of body weight, either by caloric restriction or bariatric surgery, is concurrently associated with increased gray matter volumes and white matter densities of the frontal lobes in obese adults from the general population.[46,47,48] These find-

Table 3 Correlations between brain volumes and clinical characteristics of 42 older patients with bipolar disorder.

Clinical variables	Total gray matter (%)		Total white matter (%)		Prefrontal cortex, left (%)		Prefrontal cortex, right (%)	
	r	*P*	r	*P*	r	*P*	r	*P*
Age, years	−0.45	0.01**	−0.11	0.50	−0.31	0.04*	−0.26	0.10
Duration of illness, years	−0.04	0.82	0.32	0.04*	−0.26	0.08	−0.26	0.09
Lifetime lithium use, years	0.25	0.11	0.35	0.03*	−0.05	0.74	−0.11	0.49
Body mass index, kg/m^2	−0.30	0.06	0.21	0.19	−0.49	0.001***	−0.53	0.02*
Systolic blood pressure, mmHg	−0.33	0.07	0.27	0.13	−0.64	0.001***	−0.59	0.001***
Diastolic blood pressure, mmHg	−0.01	0.98	0.01	0.95	−0.16	0.38	−0.11	0.54

Clinical variables	Orbitofrontal cortex, left (%)		Orbitofrontal cortex, right (%)		Medial frontal cortex, left (%)		Medial frontal cortex, right (%)	
	r	*P*	r	*P*	r	*P*	r	*P*
Age, years	−0.37	0.02*	−0.33	0.03*	−0.12	0.47	−0.07	0.66
Duration of illness, years	−0.33	0.03*	−0.25	0.12	−0.05	0.74	−0.16	0.32
Lifetime lithium use, years	−0.11	0.49	−0.10	0.53	−0.25	0.11	−0.19	0.22
Body mass index, kg/m^2	−0.49	0.001***	−0.54	0.001***	−0.31	0.04*	−0.41	0.01**
Systolic blood pressure, mmHg	−0.52	0.01**	−0.60	0.001***	−0.40	0.02*	−0.52	0.01**
Diastolic blood pressure, mmHg	−0.12	0.52	−0.15	0.41	−0.17	0.35	−0.06	0.75

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

Table 4 Regression model for brain volumes of 42 older patients with bipolar disorder.

Covariates	Beta	SE	*P*	Adjusted R^2
Total gray matter				
Age	−4.401	1.618	0.011*	0.171
Prefrontal cortex, left				
Body mass index	−0.038	0.010	0.001***	0.298
Age	−0.016	0.007	0.029*	
Prefrontal cortex, right				
Body mass index	−0.038	0.010	0.001***	0.257
Orbitofrontal cortex, left				
Body mass index	−0.016	0.004	0.001***	0.331
Age	−0.008	0.003	0.008**	
Orbitofrontal cortex, right				
Body mass index	−0.017	0.005	0.003**	0.420
Age	−0.009	0.004	0.018*	
Medial frontal cortex, left				
Cardiovascular disease	−0.102	0.039	0.014*	0.121
Medial frontal cortex, right				
Body mass index	−0.010	0.003	0.007**	0.147

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

ings may interestingly raise a clinical question regarding whether the neuroprogression associated with obesity in patients with BD can be reversed by weight reduction. A recent proof-of-concept, open-label trial demonstrated that adjunctive treatment with a glucagon-like peptide 1 receptor agonist significantly promoted weight loss and weight-loss-moderated volume increase in the frontal lobes of obese patients with mood disorders.[49] Our present findings also suggest the need of future research examining the neuroprotective effect of body weight reduction against the gray matter loss specific to older patients with BD.

Several methodological limitations need to be addressed when interpreting our findings. First, this study had a cross-sectional design; thus, the direction of causation could not be determined. Second, while the sample size is relatively large for an MRI study of older-age BD, it was still small. This may limit the statistical power for detecting the difference in several potential variables and the generalizability of our findings. Third, this study was hypothesis-driven. Although it yielded findings that align with prior literature, the MRI strength of 1.5T is still limited. Therefore, further research needs to use 3.0T MR scanner to examine the association between BMI/obesity and cortical volumes of other brain regions in older-age BD. Fourth, although BMI is widely used to define overweight and obesity in clinical settings, it may not distinguish between increased mass in fat and lean tissues. Future studies using additional obesity-related measures (e.g., waist circumference) are required to validate the observed associations in the present study.

In conclusion, we found that higher BMI was associated with smaller cortical volumes across the individual frontal regions among older-age BD independent of the cardiometabolic comorbidity. The findings suggest that a multidisciplinary intervention for obesity is required in aging adults with BD to reduce neuroprogression. Furthermore, future research is necessary to elucidate the mechanisms underlying the negative association between BMI and frontal cortical volumes in older-age BD.

Ethical considerations

The Taipei Medical University–Joint Institutional Review Board approved the research protocol. Appropriate procedures were followed in accordance with ethical and legal standards. All participants provided written informed consent before participation.

Conflict of interest

The authors have no conflict of interest to declare.

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