ASSOCIATIONS BETWEEN SARCOPENIC OBESITY AND COGNITIVE IMPAIRMENT IN ELDERLY CHINESE COMMUNITY-DWELLING INDIVIDUALS

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Abstract: *Introduction:* This study aimed to estimate the prevalence of sarcopenic obesity (SO) and the association between cognitive impairment and SO in a cohort of elderly Chinese community-dwelling individuals. *Methods:* A total of 948 elderly Chinese community-dwelling individuals aged 60–92 years were recruited. The participants were categorized into the following four groups according to their sarcopenia and obesity status: sarcopenic obese, sarcopenic, obese and non-sarcopenic, and non-obese group. Sarcopenia was defined as appendicular skeletal muscle index of <7.0 kg/m² in men and <5.7 kg/m² in women; obesity was defined as values greater than the upper two quintiles for body fat percentage stratified by gender of the study population; cognitive impairment was measured using the Mini-Mental State Examination and defined as a score of <24. *Results:* A total of 945 participants were included in the statistical analyses with a mean age of 68.76 ± 6.50 years. The prevalence of SO was 6.0% (7.3% in men and 4.8% in women). The sarcopenic obese (odds ratio [OR]: 2.550, 95% confidence interval [CI], 1.196-5.435) and obese (ORs: 2.141, 95% CI, 1.230-3.728) groups had significantly increased risk for cognitive impairment in fully adjusted model, respectively. *Conclusion:* The SO prevalence in elderly Chinese community-dwelling individuals was relatively low (6.0%). The present study suggested SO was independently associated with cognitive impairment.

Key words: Sarcopenia, obesity, sarcopenic obesity, cognitive impairment.

Introduction

Sarcopenia was first described by Rosenberg as an agerelated loss of skeletal muscle (1). Recently, it was considered as an age-related decline in the skeletal muscle mass and function (defined by muscle strength or physical performance) and associated with several poor health outcomes, such as physical disability, poor quality of life, impaired cardiopulmonary performance, fracture, falls, and mortality in older individuals (2). In a study of older suburban Chinese, the prevalence of sarcopenia was 6.4% in men and 11.5% in women (3). Deterioration in cognitive function occur as a neurodegenerative process of aging and may result in great economic and social burden. According to the Centers for Disease Control and Prevention, the prevalence of mild cognitive impairment (MCI) ranges from 3% to 19% in adults >65 years; meanwhile, dementia affects > 6\% of the world's population, and over 22% of individuals aged ≥85 years worldwide. In the mainland China, a total of 9.19 million cases of any cognitive impairment were reported in 2010 and the numbers are expected to increase in the coming decades (4). The risk factors for cognitive impairment include malnutrition, immune or inflammatory response, oxidative stress, and hormonal dysregulation, which are all potential causes of sarcopenia (5). Previous studies have investigated the association between sarcopenia and cognitive impairment and showed a positive relation between the two geriatric syndromes (5-7).

Moreover, except for age-related loss of muscle mass, accumulation of body fat mass may lead to obesity and increase metabolic risk factors in elderly individuals due to increased secretion of a number of pro-inflammatory cytokines (8). Unlike sarcopenia, the relationship between obesity and cognitive impairment is controversial. Some biological reasons existed on the assumption that body fat mass will be positively associated with cognitive function, and a high body mass index (BMI) is indeed found to be associated with chronic comorbidities that increase the risk of dementia. However, a meta-analysis demonstrated a U-shaped relationship between BMI and dementia risk (9). Furthermore, previous researches reported the overweight or obesity in midlife was a risk factor of dementia, while some benefits of moderate overweight at older ages were also identified (10). Given that the impact of obesity in elderly is not fully understood, more research is needed to further uncover the association between body fat and cognitive impairment. Moreover, most of the previous researches defined obesity using BMI; however, it obviously may underestimate body fat mass because of changes in the body composition and overestimate due to loss of height from vertebral compression and kyphosis. Therefore, the relationship between BMI and disease risk is much weaker in the elderly than in younger people (11, 12). A more representative

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definition is needed to identify obesity in elderly, so that we can investigate the precise association between obesity and cognitive impairment.

Sarcopenic obesity (SO), a new term for another age-related change in body composition, has become an increasing health concern in the aging society (8, 13). It was first defined by Baumgartner as a combination of low muscle mass and high body fat, especially visceral fat, and the specific prevalence rate of SO increased from approximately 2% in individuals aged between 60 and 69 years to 10% in those aged >80 years (14). These subjects may maintain a normal weight, distinct from those with sarcopenia or obesity. Some researchers have stated that SO is not only a simple combination of two pathological conditions but also an additive effect of metabolic and functional capability (15). To our knowledge, no consensus definition of SO exists, and varied combinations of body composition indices and cut-off values have been used to determine the condition in previous researches (16-21). The prevalence of SO varied significantly among different studies according to the definition applied, as well as age and nationality. Previous studies have shown that SO increased the risk of inflammation, disability, and mortality (16, 22-24). However, the study on the association between cognitive status and SO in elderly community-dwelling individuals is not yet available to date.

This study aimed to estimate (1) the prevalence of SO in a cohort of elderly Chinese community-dwelling individuals, using the muscle mass and fat mass values, and (2) the association between SO and cognitive impairment measured using Mini-mental State Examination (MMSE).

Methods

Design

A cohort was designed to determine the relationship among SO and cognitive impairment. Elderly volunteers were recruited through leaflets and posters from three communities in Chengdu City to undergo anthropometric measurements and questionnaire survey in 2014. The study staff were well trained in using investigation manuals and multimedia materials and working with simulated patients. The trained interviewers collected the data from all study participants at Yulin community centers through face-to-face interviews.

Participants

A total of 948 (465 men and 483 women) participants aged 60–92 years were recruited in the study. Volunteers with self-reported diseases (including hyperthyroidism, hypothyroidism, and chronic heart and renal failure), physical disabilities (e.g., loss of hand, foot, or limbs), and electronic devices or orthopedic metal implantations and those who are taking prescribed medications that could obviously affect body composition (e.g., long-term systemic corticosteroid) were excluded. Individuals who could not accomplish the survey

due to severe hearing or eye problems were also excluded from the study. Of all these participants, one woman with missing information on skeletal muscle mass and two women with missing data from the MMSE were excluded. A total of 945 individuals were finally analyzed (465 men and 480 women). The study was approved by the ethics committee of Sichuan University (reference No. 2014 (57)). A written consent was obtained from each participant or their representative prior to research.

Assessment of sarcopenia, obesity and SO

Whole-body composition was estimated through bioimpedance analysis (BIA) using Inbody 720 (Biospace, Seoul, Korea). According to the Asian Working Group for Sarcopenia (AWGS) algorithm (2), sarcopenia is defined as appendicular skeletal muscle index (ASMI, ASM/height2) of <7.0 kg/m² in men and <5.7 kg/m² in women. Obesity was assessed by the means of body fat percentage (BF%, fat mass/ weight). Because no consensus definition has yet been adopted (25), a standard statistical approach was used to define obesity: participants in the highest quintile of the BF% distribution. The cut-off points adjusted for gender was ≥31.61% for men and ≥40.68% for women. Based on the presence or absence of sarcopenia and obesity, participants were categorized into four nonoverlapping groups: sarcopenic obese (low muscle mass and high body fat), sarcopenic (low muscle mass and normal body fat), obese (normal muscle mass and high body fat), and nonsarcopenic and non-obese (normal muscle mass and body fat).

Assessment of cognitive impairment

Cognitive function was measured using the 30-item MMSE, which is a global test with components that include orientation, attention, calculation, language, and recall. Participants were categorized as follows: severe cognitive impairment (scores 0–17), MCI (scores 18–23), and normal (scores 24–30) (26). In our sample, only 23 participants had scores of \leq 17 (6 men and 17 women). Therefore, we included participants with MCI and severe cognitive impairment into the cognitive impaired group in data analysis.

Assessment of confounders

Demographic information included age, gender, and profession. The medical history of chronic conditions diagnosed by physicians was obtained by asking the participants or their caregivers, which included thyroid diseases, heart problems, renal diseases, hypertension, stroke, cancer, diabetes, chronic obstructive pulmonary disease (COPD), hepatic diseases, and human immunodeficiency virus. Smokers and alcohol drinkers were categorized as current or not current. Physical activity was assessed using the International Physical Activity Questionnaire-long form (27). The MET energy expenditure estimate assigned to each category of activity was calculated, and the participants were categorized into three levels: high, moderate, and low. Depressive symptoms were assessed using

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the self-reported 15-item Geriatric Depression Scale (GDS) and defined as a score of ≥5 (28). Nutritional status was evaluated using Determine, a list of 10 statements. These statements represent different common risk factors for malnutrition and are scored in relation to their importance. The total score ranged from 0 to 21, with a lower score indicating a better nutritional status, and participants with a score of ≥3 are at risk for malnutrition (29). Muscle strength was assessed by handgrip strength (HS), which was measured using a handheld dynamometer (CAMRY EH101, Zhongshan, China) to the nearest 0.1 kg. Both hands were tested three times, and the maximum value from the dominant hand was used for the analysis. Physical performance was assessed by the usual gait speed (GS) on a 6-m course. The participants were asked to walk 6 m at their usual pace, and the time required to walk the distance was measured to calculate GS. The gait test was performed twice, and the mean value was used for the analysis.

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 18.0 (IBM Corporate Headquarters, Armonk, NY). Differences between the four groups defined by sarcopenia and obesity status were compared through one-way analysis of variance (ANOVA) for continuous variables and Pearson's chi-square test or nonparametric test (with the expected cell count of <5) for categorical variables. Associations between SO and cognitive impairment were examined using multivariable logistic regression to estimate the odds ratios (ORs), comparing the sarcopenic, obese, and sarcopenic obese groups with the non-sarcopenic and non-obese group. Models were also adjusted for potential confounders, which were selected based on their association with cognitive impairment, muscle mass, and obesity. A value of p<0.05 was considered statistically significant.

Results

Characteristics of participants

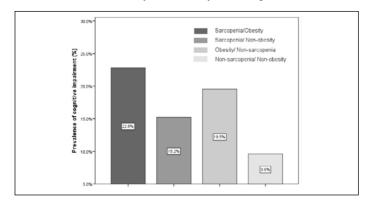
Among the 945 participants, the mean age was 68.76 ± 6.50 (range: 60-92) years, and the mean age of men and women were 69.10 ± 6.63 and 68.42 ± 6.37 years, respectively. Approximately 50.8% of participants were women, 15.1% were current smokers, and 27.2% were drinkers. Moreover, 54.4% of participants had comorbidity, and the most prevalent chronic diseases were hypertension (43.5%), diabetes (19.1%), and heart disease (5.4%).

The prevalence of SO

The prevalence of SO, sarcopenia, obesity, and non-sarcopenia and non-obesity was 6.0% (7.3% in men and 4.8% in women), 29.2% (26.5% in men and 31.9% in women), 14.1% (12.9% in men and 15.2% in women), and 50.7% (53.3% in men and 48.1% in women), respectively. A total of 127 (13.4%) participants were classified as having cognitive impairment.

The prevalence of cognitive impairment by sarcopenia and obesity status is shown in Figure 1.

Figure 1
Prevalence of cognitive impairment by sarcopenia and obesity status in the elderly community-dwelling individuals



The association between cognitive impairment and sarcopenia and obesity status

Table 1 shows the characteristics of the four groups, with the mean ages of 71.56 ± 7.49 , 69.97 ± 6.91 , 69.40 ± 6.62 , and 67.54±5.83 years, respectively (p<0.05). The participants with SO were older and had poor cognitive status compared to those without sarcopenia or obesity. The smoking status and prevalence of hypertension were different between groups. HS and GS were significantly different between the groups: those with SO had the lowest HS and sarcopenic participants had the slowest GS. We calculated the ORs using multiple logistic regression models that predict cognitive impairment adjusted for age, gender, physical activity, smoking status, alcohol consumption, number of chronic diseases, nutritional status, and depressive symptoms. The risk for cognitive impairment was significantly higher in the sarcopenic obese group compared to the optimal group in unadjusted model (ORs: 2.781, 95% CI, 1.396-5.541) and in fully adjusted model (ORs: 2.550, 95% CI, 1.196-5.435). Obese group was also significantly association with cognitive status in unadjusted model (ORs: 2.287, 95% CI, 1.353-3.868) and in fully adjusted model (ORs: 2.141, 95% CI, 1.230-3.728). The sarcopenic group had high ORs; however, the values were not statistically significant in the adjusted model (Table 2).

Discussion

Based on this cross-sectional analysis of data from 945 elderly Chinese community-dwelling individuals, the prevalence of SO was 6.0% (7.3% in men and 4.8% in women). The prevalence of cognitive impairment was significantly higher in the sarcopenic obese group than those without sarcopenia and obesity, and merely with sarcopenia or obesity. The present study also identified the positive association between SO and cognitive function after adjusting the potential confounders.

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 Table 1

 Characteristics of participants by sarcopenia and obesity status

		Sarcopenic Obesity	Sarcopenia (Non-obesity)	Obesity (Non- sarcopenia)	Non- sarcopenia and Non-obesity	p
n(n,%)		57(6.0)	276(29.2)	133(14.1)	479(50.7%)	=
Age(y)		71.56±7.49	69.97±6.91	69.40±6.62	67.54±5.83	< 0.001
Female(n,%)		23(40.4)	153(55.4)	73(54.9)	231(48.2)	0.071
Smoker		12(21.1)	45(16.3)	4(3.0)	82(17.1)	< 0.001
Alcohol drinker		17(29.8)	62(22.5)	41(30.8)	137(28.6)	0.197
Physical activity						0.080
	Low	1(1.8)	11(4.0)	5(3.8)	7(1.5)	
	Moderate	21(37.5)	102(37.0)	39(29.3)	144(30.1)	
	High	34(60.7)	163(59.1)	89(66.9)	327(68.4)	
Chronic comorbio	dity					
	Hypertension	25(43.9)	8(35.5)	78(59.1)	210(43.8)	< 0.001
	Diabetes	8(14.0)	49(17.8)	25(18.8)	98(20.5)	0.603
	Heart disease	2(3.5)	16(5.8)	5(3.8)	27(5.6)	0.744
Number of chronic comorbidity*		0.73±0.5	0.69±0.89	0.86±0.78	0.76±0.83	0.253
BMI (kg/m²)		24.99±1.47	21.01±2.02	28.04±2.39	24.33±2.10	<0.000
BF% (%)		37.68±4.73	28.66±6.88	39.43±4.89	29.81±6.44	<0.000
ASMI (kg/m²)		6.17±0.69	5.82±0.72	7.01±0.87	7.01±0.83	<0.000
MMSE score		25.36±3.74	26.33±3.18	26.02±3.30	26.91±2.72	<0.000
HS(kg)		27.48±7.37	26.27±7.30	29.35±9.35	32.45±8.87	<0.000
GS(m/s)		0.96±0.19	1.03±0.20	1.01±0.18	1.08±0.18	<0.000
Determine score		1.79±1.62	2.00±2.02	1.68±1.89	1.80±1.82	0.352
GDS score		1.93±1.64	1.87±2.18	1.51±1.67	1.53±1.84	0.075

Mean and standard deviation are shown for continuous variables, proportions as percent are shown for categorical variables; Using one-way analysis of variance (ANOVA) for continuous variables and the Pearson chi-square test or Nonparametric test (for which an expected cell count was <5) for categorical variables; Abbreviations: BMI, body mass index; GS, gait speed; HS, handgrip strength; BF%, body fat percentage; ASMI, appendicular skeletal muscle mass index; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; During testing, p<0.05 was considered statistically significant; * Chronic comorbidity investigated in the study included thyroid diseases, heart problems, renal diseases, hypertension, stroke, cancer, diabetes, chronic obstructive pulmonary disease, hepatic diseases, and acquired immune deficiency syndrome

Table 2

Multivariable Logistic Regression model for the risk of cognitive impairment according to obesity and sarcopenia status

	Sarcopenia				Non-sarcopenia			
	Obesity		Non-obesity		Obesity		Non-obesity	
	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p		
model 1	2.781(1.396-5.541)	0.004	1.690(1.080-2.643)	0.022	2.287(1.353-3.868)	0.002	-	
model 2	2.404(1.169-4.944)	0.017	1.405(0.885-2.230)	0.149	2.012(1.176-3.444)	0.011	-	
model 3	2.544(1.229-5.265)	0.012	1.403(0.878-2.241)	0.157	2.042(1.190-3.502)	0.010	-	
model 4	2.550(1.196-5.435)	0.015	1.355(0.828-2.218)	0.227	2.141(1.230-3.728)	0.007	-	

Non-sarcopenia and Non-obesity group is the reference group; Abbreviations: OR, odds ratio; CI, confidence interval; model 1: unadjusted; model 2: adjusted for age and gender; model 3: adjusted for age, gender, smoking status, alcohol drinking status, physical activity and chronic comorbidity burden; model 4: adjusted for age, gender, smoking status, alcohol drinking status, physical activity, chronic comorbidity burden, nutritional condition and depressive status

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Well-accepted diagnostic criterion for SO is lacking and various diagnostic definitions of SO were used in previous studies. Baumgartner defined SO as an SMI of two standard deviations below the sex-specific mean value for a younger reference group and a total fat percentage higher than the median for each gender; and first reported a prevalence of 3.7% in the New Mexico Elder Health Survey (NMEHS) (14) and 5.8% in the New Mexico Aging Process Study (NMAPS) (16). However, a few recent SO studies used diagnostic criteria based on muscle strength (30) or combination of muscle mass, strength, and physical performance (31, 32). Although, muscle strength and physical performance have been well documented as better predictors of mortality for sarcopenic individuals, no evidence could confirm that they are also better in the definition of SO to date. Hence, we defined SO as a combination of low appendicular muscle mass and high BF%. To date, a few studies have evaluated the prevalence of SO in Chinese population. In 2014, Meng et al. (31) defined sarcopenia according to the EWGSOP criteria and obesity using BMI. They first reported the prevalence of SO of 4.9% and 11.5% using SMI or percentage skeletal muscle index among Chinese men aged ≥80 years, respectively. However, in the present study, sarcopenia was defined as ASMI of <7.0 kg/m² in men and <5.7 kg/m² in women according to the AWGS algorithm, and obesity was defined as values greater than the upper two quintiles for BF% of the study population. The prevalence of SO was 6% in Chinese community-dwelling elderly patients. Batsis (33) surveyed the non-institutionalized persons in the United States and also reported a considerably different prevalence. Kim (19) employed to use several different indices to define SO in the same population, and the prevalence varied between 1.3% and 23% for men and 0.8% and 16.5% for women. The tremendous variation could be due to the diverse nationality of participants in each study and the lack of uniform diagnostic criteria. Moreover, the difference in age was another possible reason for the diverse prevalence: in Meng's research, only 101 men were included with a mean age of 88.8±3.7 years; the population in our study was much younger with the mean age of 68.76±6.50 years.

Some previous studies have estimated the association between cognitive impairment and sarcopenia, and a recent systematic review reported sarcopenia was independently associated with cognitive impairment (ORs: 2.246, 95% CI, 1.210-4.168) (7). However, all literature included in the review used a cross-sectional design, so the causal relationships were vague, which required future cohort studies to clarify. Additionally, these studies used various definitions of sarcopenia. In the present study, ASMI alone was used to define sarcopenia, instead of the combination of muscle mass and strength or physical performance. Meanwhile, if sarcopenia was classified according to AWGS algorithm in this study, it was also significantly associated with cognitive impairment in the fully adjusted model (not reported). Moreover, our study also found cognitive impairment was more prevalent

in obese participants (ORs: 2.141, 95% CI: 1.230–3.728, p<0.05). Several studies on the association between cognitive deterioration and obesity were already conducted, but the results were conflicting. An 18-year prospective cohort study suggested that overweight with increased age is a risk factor for dementia, particularly in women (34). Whitmer et al. (35) verified that central obesity in midlife contributes to cognitive impairment through a more than 3-decade follow-up, and a similar result was suggested by other researches (36). In contrast, another prospective population-based study conducted in Finland showed that high BMI scores in late life should not be considered as a risk factor for dementia (37). The results varied across studies because of different population groups, ages, gender, and definition of obesity. Thus, further studies should be conducted to verify these findings.

Our primary hypothesis was that SO was linked to a higher prevalence of cognitive impairment than either sarcopenia or obesity alone. The present study did find that sarcopenic obese group had a 2.5 fold increased risk for cognitive impairment even after the adjustment for confounders, such as age, gender, physical activity, nutritional status, and depressive symptoms. The observed association did not diminish after the adjustment for potential confounders, but a greater risk remained, suggesting that these variables only partially explain the relationship between SO and cognitive impairment. A vicious cycle may exist between the accumulation of fat and loss of skeletal muscle mass since they have a reciprocal influence on each other (38). What then is the mechanism underlying this link? We proposed that some mechanisms linked muscle mass and fat mass with the brain to affect cognitive function. The possible mechanisms are as follows: first, systemic inflammation and insulin resistance may play a part in the concurrence of SO and cognitive impairment (39). Previous studies have verified the association between executive dysfunction and elevated serum levels of C-reactive protein and interleukin-6 (IL-6), which implies that chronic inflammation may play a potential role in cognitive impairment (40, 41). Furthermore, chronic inflammation is associated with the development of SO. Pro-inflammatory cytokines, such as IL-6, tumor necrosis factor-α, and adipokines (leptin and adiponectin), were positively associated with fat mass and negatively associated with muscle mass (42). Second, previous studies showed that sarcopenic obese individuals had decreased growth hormone secretion (43), and replacement therapy, particularly the use of growth hormone-releasing hormone, improved cognitive function (44) and increases muscle strength (45). This suggests that participants with both cognitive impairment and sarcopenia may have the same hormonal deficits. Third, insulin resistance has been identified as a factor facilitating the maintenance of SO and cognitive impairment. Insulin resistance in obese individuals may promote muscle catabolism and lead to muscle mass loss or sarcopenia because insulin is a powerful anabolic signal that delivers protein metabolism (42). At the same time, the

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loss of muscle reduces the mass of available insulin-responsive target tissues, which aggravates insulin resistance and promotes sarcopenia and obesity (46). Furthermore, higher insulin resistance has been found to be associated with poorer cognitive efficiency, executive dysfunction, and worse brain function (47-49). However, we did not measure these factors in the present study; thus, whether SO increases cognitive impairment via the abovementioned mechanisms requires further studies.

Our study had several limitations. First, participants were recruited through leaflets and posters instead of random selection. This recruitment method resulted in the exclusion of elderly individuals with severe frailty or disability and inevitably led to a selection bias. We may have underestimated the prevalence of SO, therefore the results should be cautiously interpreted. Second, the cross-sectional nature of this study did not allow identification of causal relationships as those of a longitudinal or semi-longitudinal study. Therefore, future studies with a prospective longitudinal cohort design should be conducted to establish a causal relationship between SO and cognitive impairment. Third, we estimated muscle mass using BIA. Although BIA is easily implemented in largescale population-based studies, it may not be as accurate as dual-energy X-ray absorptiometry (DEXA). However, the correlation between BIA and DEXA has been high in the Chinese elderly population (50); furthermore, BIA and DEXA are both recommended by the AWGS in clinical practice, it is the most feasible and appropriate choice for our research. Fourth, concerning the challenge due to obvious muscle mass loss and fat gain in elderly individuals, we used BF% to determine obesity, instead of BMI which is the most frequently used index for obesity according to WHO recommendation. However, there is a lack of generally accepted reference value in the Chinese elderly population.

Conclusion

In summary, we examined the prevalence of SO in elderly Chinese community-dwelling individuals by ASMI and BF% and found that it was similarly low (6.0%). The considerable difference between studies depends on nationality, age, and definition of SO. We also found significant association between SO and cognitive impairment after adjusting for potential confounders. Considering that SO has an additive effect on cognitive functional deterioration than sarcopenia and obesity individually, a standardized definition is necessary, and more strategies should be developed to prevent or control SO.

Conflict of Interest: Hui Wang, Shan Hai, Yixin Liu, Cao Li, Ying Liu, Ping Liu, Ying Yang, and Birong Dong declare that they have no conflict of interest.

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Ethical standards: This study complies with the current laws of China and the requirements of the Declaration of Helsinki. The protocol of study was approved by the ethics committee of Sichuan University (reference No. 2014 (57)).

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