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ORIGINAL ARTICLE

Serum Uric Acid Levels and the Risk of Obesity: a Longitudinal Population-Based Epidemiological Study

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SUMMARY

Background: **Obesity is a common chronic disease, and elevated serum uric acid has been suggested to be associated with obesity. However, whether the elevation is casual or a consequence of obesity remains unclear. We performed the study to investigate the longitudinal association between serum uric acid levels and obesity.**
Methods: **A total of 4411 initially obesity-free subjects were followed up for 9 years. The subjects were divided into groups according to the serum uric acid quartile. Univariable and multivariable Cox regression models were used to analyze the risk factors for the development of obesity.**
Results: **Of the 4411 subjects, 1272 (28.8%) subjects developed obesity over 9 years of follow-up. The cumulative incidence of obesity was 21.7%, 26.4%, 31.0%, and 36.4% in quartile 1, 2, 3 and 4, respectively (p for trend < 0.001). Cox regression analyses indicated that serum uric acid levels were independently and positively associated with the risk of incident obesity.**
Conclusions: **Our longitudinal study demonstrated that high serum uric acid levels increase the risk of obesity.**
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KEY WORDS

obesity, serum uric acid, association

INTRODUCTION

Obesity is a chronic disease consisting of the increase in body fat stores and it has been paid close attention and become a major global public health problem in recent decades [1]. The prevalence of obesity in the world has continued to increase in recent years. According to the World Health Organization (WHO), the prevalence of obesity among adults is more than 10% in the world [2]. And the prevalence of overweight and obesity among Chinese adults in 2010 was 30.6% and 12.0%, respectively [3]. Recent investigations have suggested that obesity is closely associated with many chronic diseases, such as cardiovascular disease (CVD) [4], type 2 diabetes mellitus (DM) [5], and so on. However, the exact risk factors for obesity have not been fully clarified.

As the end product of purine metabolism, serum uric acid (SUA) was associated with hypertension (HTN), dyslipidemia, coronary artery disease, and metabolic syndrome [6-9]. A recent cross-sectional study showed that elevated uric acid may be associated with obesity [10]. However, no consistent conclusion has been reached regarding serum uric acid and obesity at present.

Therefore, we performed a longitudinal population-based study in order to investigate whether the elevation of serum uric acid has a causal role for obesity among Chinese population.

MATERIALS AND METHODS

Study population

To identify whether serum uric acid plays a causal role in development of obesity, a population-based longitudinal study was conducted among the petrochemical employees of Zhenhai Refining & Chemical Company Ltd. in the city of Ningbo, China, from 2006 to 2015. Certain participants were excluded at study entry: (I) individuals diagnosed with obesity. (II) Individuals using drugs to lower weight, serum lipids, uric acid or blood pressure. (III) Individuals with a positive history of known liver diseases. A total of 4411 initially obesity-free subjects (2889 males and 1522 females) were evaluated for the development of obesity.

Data collection and measurements

Data were obtained in the health check-up center of Zhenhai Refining & Chemical Company Ltd. All participants completed a questionnaire, including demographic characteristics, smoking status, alcohol consumption, and medical history under the supervision of physicians who were well-trained.

Height and weight were measured with light clothing without shoes for each subject. BMI was calculated as weight (kg) per height (m) squared. Waist circumference (WC) was measured around the smallest circumference with the measuring tape positioned between the ribs and iliac crest. Current smoking was defined as people who had smoked more than 100 cigarettes in their lifetime and currently smoking. Current drinking was defined as drinking more than once per month during the past twelve months. Sitting blood pressure was measured from the right arm three times with a 1-min interval between the measurements after resting for 20 minutes, using an automated device (Omron HEM-7052; Omron Corp., Kyoto, Japan). The mean of three measurements was calculated for analysis.

Blood samples, which were used to analyze the biochemical index, were obtained from the participants in the morning after at least a 10-hour fast. All the laboratories involved resoundingly completed the standardization. Triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), serum uric acid (SUA), fasting plasma glucose (FPG), and some blood routine indices (e.g., Hs-CRP, etc.) were estimated using an Olympus AU640 auto-analyzer (Olympus, Kobe, Japan).

Definitions

Obesity was defined as BMI $\geq$ 25 kg/m^2 based on the Asian-Pacific World Health Organization (WHO) criteria [11]. The subjects who had three or more of the following abnormalities were diagnosed as Metabolic syndrome: (I) raised blood pressure, systolic blood pressure (SBP) $\geq$ 130 mmHg or diastolic blood pressure (DBP) $\geq$ 85 mmHg, or treatment of previously diagnosed hypertension; (II) raised FPG, defined as FPG $\geq$ 6.1 mmol/L, or previously diagnosed diabetes; (III) raised triglyceride level, defined as triglycerides $\geq$ 1.7 mmol/L; (IV) reduced HDL-C, defined as HDL-C < 1.0 mmol/L; (V) WC $\geq$ 90 cm for Chinese men and $\geq$ 85 cm for Chinese women [12]. The estimated glomerular filtration rate (eGFR) was calculated using the improved Chinese population MDRD formula [13].

Statistical analysis

The subjects were stratified according to their serum uric acid levels: quartile 1 ($\leq$ 302 μmol/L), quartile 2 (303 - 343 μmol/L), quartile 3 (344 - 388 μmol/L), and quartile 4 ($\geq$ 389 μmol/L) for male; and quartile 1 ($\leq$ 209 μmol/L), quartile 2 (210 - 243 μmol/L), quartile 3 (244 - 282 μmol/L), and quartile 4 ($\geq$ 283 μmol/L) for female. The baseline characteristics of the subjects in each quartile were compared. The cumulative incidence of obesity was calculated by dividing the number of cases by the numbers of subjects followed up for each serum uric acid quartile.

Cox proportional hazards regression was used to estimate hazard ratios for incident obesity for each baseline serum uric acid quartile. For linear trends of risk, the number of quartiles was used as a continuous variable and tested on each model.

The fundamental characteristics of the sample were summarized by descriptive statistics. In addition, the data for continuous variables were expressed as median (IQR) and the data for categorical variables were presented as percentages (%). Continuous variables were compared using the Student's *t*-test, Mann-Whitney *U* test, Kruskal-Wallis *H* test or one-way ANOVA depending on the normality of the data. Categorical variables between groups were compared using Chi-square test. For a statistical inference, all p-values are bilateral, and a p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 17.0, SPSS software, Chicago, IL, USA).

Table 1. Baseline characteristics of the subjects according to serum uric acid quartiles.

Variables	All subjects (n = 4411)	Serum uric acid quartile				
		Quartile 1 (n = 1113)	Quartile 2 (n = 1106)	Quartile 3 (n = 1107)	Quartile 4 (n = 1085)	p
Gender (male/%)	2889/65.5	730/65.6	725/65.6	721/65.1	713/65.7	0.99
Age (years)	41.0 (34.0 - 51.0)	41.0 (34.0 - 50.0)	40.0 (33.0 - 49.0)	41.0 (34.0 - 50.0)	42.0 (35.0 - 53.0)	< 0.001
BMI (kg/m2)	22.0 (20.3 - 23.5)	21.2 (19.7 - 22.8)	21.7 (20.0 - 23.3)	22.2 (20.4 - 23.5)	22.7 (21.1 - 23.9)	< 0.001
SBP (mmHg)	118.0 (109.0 - 127.0)	116.0 (106.0 - 125.0)	116.0 (107.0 - 125.0)	118.0 (109.0 - 128.0)	120.0 (112.0 - 130.0)	< 0.001
DBP (mmHg)	75.0 (69.0 - 81.0)	73.0 (67.0 - 80.0)	74.0 (68.0 - 80.0)	75.0 (70.0 - 81.0)	77.0 (71.0 - 83.0)	< 0.001
WC (cm)	76.0 (70.0 - 81.0)	74.0 (68.0 - 79.0)	75.0 (69.0 - 81.0)	76.0 (71.0 - 82.0)	78.0 (73.0 - 83.0)	< 0.001
UREA (mmol/L)	4.93 (4.19 - 5.77)	4.74 (4.02 - 5.53)	4.87 (4.16 - 5.74)	5.00 (4.24 - 5.76)	5.15 (4.40 - 5.99)	< 0.001
CREA (µmol/L)	71.0 (60.0 - 81.0)	69.0 (57.5 - 77.0)	71.0 (59.0 - 80.0)	72.0 (61.0 - 81.0)	74.0 (64.0 - 84.0)	< 0.001
FPG (mmol/L)	4.43 (4.14 - 4.77)	4.43 (4.14 - 4.77)	4.41 (4.13 - 4.74)	4.42 (4.13 - 4.75)	4.46 (4.14 - 4.83)	0.057
SUA (µmol/L)	315.0 (258.0 - 371.0)	256.0 (198.0 - 285.0)	317.0 (234.0 - 334.0)	357.0 (270.0 - 374.0)	409.0 (338.0 - 441.0)	< 0.001
AST (U/L)	19.0 (16.0 - 23.0)	18.0 (16.0 - 22.0)	19.0 (16.0 - 23.0)	19.0 (17.0 - 23.0)	20.0 (17.0 - 24.0)	< 0.001
ALT (U/L)	21.0 (15.0 - 30.0)	19.0 (14.0 - 27.0)	20.0 (15.0 - 29.0)	21.0 (16.0 - 31.0)	23.0 (17.0 - 34.0)	< 0.001
TC (mmol/L)	4.66 (4.08 - 5.29)	4.56 (4.01 - 5.14)	4.58 (4.03 - 5.21)	4.66 (4.09 - 5.30)	4.84 (4.19 - 5.49)	< 0.001
TG (mmol/L)	1.14 (0.84 - 1.64)	1.00 (0.77 - 1.32)	1.05 (0.81 - 1.49)	1.21 (0.87 - 1.71)	1.42 (1.01 - 1.98)	< 0.001
HDL-C (mmol/L)	1.29 (1.09 - 1.59)	1.32 (1.09 - 1.64)	1.30 (1.09 - 1.61)	1.29 (1.08 - 1.57)	1.27 (1.09 - 1.53)	0.009
LDL-C (mmol/L)	2.57 (2.09 - 3.09)	2.49 (2.04 - 3.01)	2.52 (2.08 - 3.04)	2.57 (2.06 - 3.08)	2.72 (2.21 - 3.25)	< 0.001
eGFR (mL/ (min·1.73 m2))	110.8 (98.9 - 125.5)	116.5 (104.7 - 132.2)	112.3 (100.2 - 126.5)	109.3 (97.9 - 123.6)	105.3 (93.4 - 117.6)	< 0.001

Data are presented as median (IQR). p-values are based on Chi-square text for categorical data and on Kruskal-Wallis H test or one-way analysis of variance for continuous data, depending on the normality of the data.

RESULTS

Characteristics of the participants

A total of 4411 subjects including 2889 (65.5%) males and 1522 (34.5%) females were evaluated yearly over the course of the study. The baseline clinical characteristics of the subjects in each serum uric acid quartile are presented in Table 1. Only the gender and FPG were not significantly different among the subjects with all four quartiles ($p > 0.05$). Age, SBP, DBP, BMI, WC, UREA, CREA, AST, ALT, TC, TG, and LDL-C all tended to increase at higher serum uric acid levels ($p < 0.05$), whereas HDL-C and eGFR decreased as the uric acid increased ($p < 0.05$).

Association between serum uric acid and incident obesity

According to the baseline serum uric acid levels, the participants were stratified into quartiles. During a total of 4411 person-years of follow-up, 1272 subjects including 978 males and 294 females developed obesity, corresponding to 33.9% and 19.3% cumulative incidence of obesity in male and female, respectively. In addition, we observed that baseline serum uric acid quartiles predicted the incidence of obesity in a positive and dose-responsive manner (Figure 1). The overall 9-year cumulative incidence of obesity was 28.8%, ranging from 21.7% in quartile 1 to 26.4%, 31.0% and 36.4% in quartile 2, quartile 3, and quartile 4, respec-

Table 2. Baseline characteristics of the subjects according to follow-up outcomes.

Variables	Subjects developed obesity (n = 1272)	Subjects did not develop obesity (n = 3139)	p
Gender (male/female, n)	978/294	1911/1228	< 0.001
Age (years)	42.0 (34.0 - 52.0)	41.0 (34.0 - 52.0)	0.485
BMI (kg/m2)	23.0 (21.2 - 24.8)	21.7 (19.9 - 23.8)	< 0.001
SBP (mmHg)	120.0 (112.0 - 130.0)	117.0 (107.0 - 127.0)	< 0.001
DBP (mmHg)	76.0 (70.0 - 83.0)	74.0 (68.0 - 81.0)	< 0.001
WC (cm)	79.0 (73.0 - 85.0)	74.0 (69.0 - 81.0)	< 0.001
UREA (mmol/L)	5.08 (4.30 - 5.97)	4.96 (4.24 - 5.82)	0.007
CREA (μmol/L)	73.0 (61.0 - 82.0)	70.0 (59.0 - 80.0)	< 0.001
FPG (mmol/L)	4.48 (4.17 - 4.84)	4.43 (4.14 - 4.77)	0.840
SUA (μmol/L)	328.0 (276.0 - 383.0)	297.0 (241.0 - 352.0)	< 0.001
AST (U/L)	20.0 (17.0 - 23.0)	19.0 (16.0 - 22.0)	< 0.001
ALT (U/L)	23.0 (17.0 - 32.0)	19.0 (14.0 - 27.0)	< 0.001
TC (mmol/L)	4.79 (4.18 - 5.42)	4.50 (3.98 - 5.10)	0.027
TG (mmol/L)	1.27 (1.05 - 1.47)	0.91 (0.73 - 1.14)	< 0.001
HDL-C (mmol/L)	1.23 (1.06 - 1.52)	1.36 (1.11 - 1.67)	< 0.001
LDL-C (mmol/L)	2.78 (2.29 - 3.27)	2.47 (2.01 - 2.98)	< 0.001
eGFR (mL/(min·1.73 m2))	108.9 (97.2 - 123.3)	111.3 (98.9 - 126.6)	< 0.001

Table 3. Univariable and multivariable Cox Proportional Hazard models of development of obesity during 9-year follow-up.

Variables	Univariable models	p-value	Multivariable models	p-value
	HR (95% CI)		HR (95% CI)	
Gender (male)	1.91 (1.67 - 2.17)	< 0.001	1.29 (1.11 - 1.50)	0.001
Age (years)	1.00 (1.00 - 1.00)	0.44	1.00 (1.00 - 1.00)	0.52
SBP (mmHg)	1.02 (1.02 - 1.02)	< 0.001	1.01 (1.01 - 1.02)	< 0.001
DBP (mmHg)	1.03 (1.03 - 1.04)	< 0.001	1.01 (1.00 - 1.02)	0.007
Smoking	1.02 (0.95 - 1.04)	0.41	1.00 (0.90 - 1.01)	0.74
Drinking	1.00 (0.92 - 1.07)	0.56	1.00 (0.98 - 1.12)	0.82
UREA (mmol/L)	1.07 (1.02 - 1.11)	0.003	1.02 (0.97 - 1.07)	0.43
CREA (μmol/L)	1.01 (1.00 - 1.01)	< 0.001	1.00 (1.00 - 1.01)	0.12
FPG (mmol/L)	1.05 (0.98 - 1.13)	0.17	1.01 (0.94 - 1.10)	0.73
AST (U/L)	1.01 (1.00 - 1.01)	< 0.001	0.98 (0.97 - 0.99)	0.001
ALT (U/L)	1.00 (1.00 - 1.01)	< 0.001	1.01 (1.01 - 1.02)	< 0.001
TC (mmol/L)	1.09 (1.03 - 1.15)	0.005	1.39 (1.10 - 1.75)	0.006
TG (mmol/L)	1.22 (1.17 - 1.26)	< 0.001	1.02 (0.95 - 1.09)	0.59
HDL-C (mmol/L)	0.49 (0.42 - 0.57)	< 0.001	0.39 (0.29 - 0.54)	< 0.001
LDL-C (mmol/L)	1.21 (1.13 - 1.29)	< 0.001	0.83 (0.65 - 1.05)	0.12
eGFR (mL/(min·1.73 m2))	0.99 (0.99 - 1.00)	< 0.001	1.00 (1.00 - 1.00)	0.74
Serum uric acid (μmol/L)		< 0.001		< 0.001
Quartile 1	1.00 (reference)		1.00 (reference)	
Quartile 2	1.24 (1.04 - 1.47)		1.18 (0.99 - 1.40)	
Quartile 3	1.49 (1.26 - 1.76)		1.29 (1.09 - 1.53)	
Quartile 4	1.83 (1.56 - 2.14)		1.47 (1.24 - 1.74)	

Table 4. Risk of development obesity according to baseline serum uric acid quartiles in unadjusted and adjusted models.

Models	Quartile of baseline serum uric acid hazard ratio (95% CI)				
	Quartile 1 (n = 1113)	Quartile 2 (n = 1106)	Quartile 3 (n = 1107)	Quartile 4 (n = 1085)	p
Unadjusted	1.00 (reference)	1.24 (1.04 - 1.47)	1.49 (1.26 - 1.76)	1.83 (1.56 - 2.14)	< 0.001
Adjusted for age and gender	1.00 (reference)	1.24 (1.04 - 1.46)	1.50 (1.27 - 1.77)	1.83 (1.56 - 2.15)	< 0.001
Adjusted for age, gender, and indictors of MS [a]	1.00 (reference)	1.21 (1.02 - 1.43)	1.39 (1.18 - 1.64)	1.65 (1.41 - 1.94)	< 0.001
Adjusted for all clinical [b] factors, smoking and drinking	1.00 (reference)	1.18 (0.99 - 1.40)	1.29 (1.09 - 1.53)	1.47 (1.24 - 1.74)	< 0.001

[a] Including age, gender, WC, SBP, DBP, HDL-C, and FPG.
[b] Including age, gender, WC, BMI, SBP, DBP, TC, HDL-C, LDL-C, FPG, UREA, CREA, AST, ALT, eGFR, smoking, and drinking.

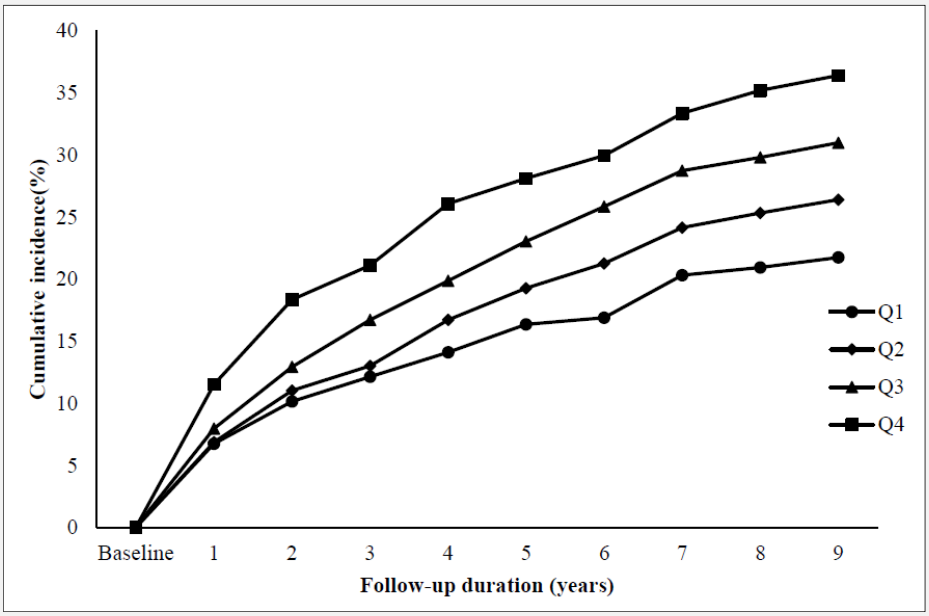

Figure1. The association between baseline serum uric acid and the cumulative incidence of obesity.

tively (p for trend < 0.001; Figure 1). This tendency also held true for 1- to 9-year cumulative incidences. These results indicated that those with higher baseline serum uric acid levels were more likely to develop obesity than those with lower levels.

Compared with the subjects without incident obesity, those with incident obesity were predominantly male, and the baseline WC, BMI, SBP, DBP, UREA, CREA, SUA, AST, ALT, lipids, and eGFR were significantly different between two groups (Table 2).

High serum uric acid increases the risk of obesity

Univariable and multivariable Cox proportional hazards regression models were used to analyze the risk of incident obesity. In univariate models, gender, SBP, DBP, UREA, CREA, AST, ALT, TC, TG, HDL-C, LDL-C, eGFR, and serum uric acid were independent factors related with incident obesity (Table 3). In multivariable

models, only gender, SBP, DBP, AST, ALT, TC, HDL-C, and serum uric acid were correlated with incident obesity (Table 3). Hazard ratio for incident obesity was also analyzed in each serum uric acid quartile, with the first quartile serving as the reference group. Compared to the first quartile, the hazard ratios (95% CI) for subjects in quartile 2, quartile 3, and quartile 4 were 1.24 (1.04 - 1.46), 1.50 (1.27 - 1.77), and 1.83 (1.56 - 2.15), respectively (p for trend < 0.001), after adjustment for age and gender. The same relationship between serum uric acid and incident obesity remained even after adjustment for indictors of MS or the clinical factors including age, gender, WC, BMI, SBP, DBP, TC, HDL-C, LDL-C, FPG, UREA, CREA, AST, ALT, eGFR, smoking, and drinking (Table 4). These findings indicated serum uric acid is associated with an increased risk of subsequent incident obesity.

DISCUSSION

Previous cross-sectional studies of higher serum uric acid and its positive association with obesity have been conducted [10,14]. However, the cause-and-effect association between serum uric acid levels and obesity could not be addressed due to the cross-sectional design of the study. Our longitudinal population-based findings expand the observation to establish the temporal sequence between serum uric acid and the later risk of obesity. Our results indicated that those with higher baseline serum uric acid were more likely to develop obesity during the follow-up period. Univariable and multivariable regression analysis suggested that participants with baseline serum uric acid levels in the fourth quartile were significantly associated with a higher risk of incident obesity after the adjustment for confounders. These observations demonstrated that serum uric acid level is an independent factor that predicts the development of obesity, and the risk increases with the rise in baseline serum uric acid levels.

There are various hypotheses as to the mechanism by which serum uric acid participates in the development of obesity. The first is that a large amount of free radicals are formed along with the serum uric acid generation during the purine metabolic process, which, in the end, leads to HDL-C oxidation, lipid peroxidation, and lipid metabolism disorders [15]. Meanwhile, the other explanation is that higher serum uric acid is often accompanied by the low activity of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and the delayed metabolism of 3-glyceraldehyde phosphate, which stimulates the de novo synthesis of ribose-5-phosphate to phosphoribosylpyrophosphate through the common metabolic pathway of NADH-NADPH, resulting in the increase of the triglyceride levels and obesity [16-18]. At present, higher serum uric acid has been a well-known risk factor for the development of various clinical diseases, such as hypertension [19], CKD [20], diabetes mellitus [21], stroke [22], and so on. Our results indicated that serum uric acid predicted the subsequent occurrence of obesity in a positive and dose-dependent manner. Therefore, the early detection of serum uric acid may be beneficial for the prevention of obesity. Certain strengths exist in our study. This longitudinal study provided important epidemiological evidence for the association between serum uric acid and incident obesity in Ningbo, China. Moreover, the 9-year longitudinal population-based study was the main strength, and the selection bias is less likely to appear in the present study as annual health check-ups in state-owned companies are mandatory in China. However, some limitations also exist in our study. First, our data was from a large-scale, state-owned plant, which may differ from the general population. Second, dietary and lifestyle information was not collected. Further studies should be required to clarify these above factors.

CONCLUSION

In summary, our population-based study showed that uric acid levels independently predicted incident obesity after adjustment for variables known to be related with obesity and suggested that a high normal serum uric acid level should be closely monitored, which may decrease the incidence of obesity.

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Ethics approval and consent to participant:
The study was performed in accordance with the guidelines of the Declaration of Helsinki. The study protocol and the form of consent were approved by the Ethics Committee of the Institutional Review Board of Zhenhai Refining & Chemical Company Ltd. and Affiliated Hospital of Ningbo University School of Medicine. Written informed consent was obtained from all participants before our gathering of data and the study.

Authors' Contributions:
RJZ carried out the study design, analysis and interpretation of data, and drafted the manuscript. CXC, TMY, QMC, and RDL participated in the study and the acquisition of data. YSM conceived the study, participating in its design and coordination, and helped in drafting the manuscript. All authors read and approved the final manuscript.

Declaration of Interest:
None declared.

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