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Association between the uric acid and hypertension in community-based Chinese population: stratified analysis based on body mass index and age

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Abstract
Many studies have shown that uric acid was related to hypertension. However, the association dependence on body mass index (BMI) or age was unclear. This study was performed with a group of 4012 Chinese population aged 30 to 92 years old. Subjects were divided into four groups according to the quartiles of uric acid (UA) concentration [First group: ≤ 231 μmol/L (reference), Second group: 231-289 μmol/L, Third group: 289-362 μmol/L, Fourth group: > 362 μmol/L]. Hypertension was defined as newly measured blood pressure ≥ 140/90 mmHg or taking antihypertensive drugs. Stratified analysis based on BMI (< 28 kg/m^2 vs ≥ 28 kg/m^2) and age (< 60 years old vs ≥ 60 years old) to analyze the association between UA and hypertension. Subjects were 54.50 (45.00, 63.00) years old, and 40.98% were male, 38.33% were hypertension. Adjusted odds ratios (95% confidence intervals) for the association of UA and hypertension were 2.226 (1.662, 2.980), 4.340 (3.253, 5.790), 5.898 (4.434, 7.845) and 6.557 (4.927, 8.727) in the four groups among ≥ 60 years old respectively comparing with first group among < 60 years old. Adjusted odds ratios (95% confidence intervals) for the association between UA and hypertension were 2.170 (1.236, 3.808), 5.260 (3.267, 8.468), 9.056 (5.509, 14.888) and 3.730 (2.529, 5.550) in the four groups among BMI ≥ 28 kg/m^2 respectively comparing with first group among BMI < 28 kg/m^2. Uric acid was significantly associated with the hypertension. The association was stronger among subjects ≥ 60 years old or BMI ≥ 28 kg/m^2.

Keywords Uric acid (UA) · Hypertension · Chinese population · Cross-sectional study

Abbreviations

UA	Uric acid
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
ALT	Alanine aminotransferase
BUN	Blood urea nitrogen
Cr	Creatinine
TG	Triglyceride
TC	Total cholesterol
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
ApoA	Apolipoprotein A
ApoB	Apolipoprotein B
CPR	C-reactive protein
FBG	Fasting blood glucose
Hcy	Homocysteine

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Highlights

- Our study was a cross-sectional study.
- We selected 4012 permanent residents in 24 rural and urban communities as research objects in Hunan Province.
- The study subjects were divided into four groups according to the quartiles of uric acid.

Introduction

Hypertension is a global health challenge, affecting millions of people around the world [1, 2]. Previous study showed that the incidence of hypertension in the world has reached 26% [3], and in China has reached 29.6% [4]. Hypertension is one of the most important risk factors for cardiovascular disease, stroke and kidney disease, and it is also the main cause of premature death and disability [5–7]. As we all know, hypertension is considered to be a multifactorial chronic disease, which may be related to some risk factors [8]. In recent years, accumulated epidemiological and clinical evidence has shown that UA level was related to hypertension [9–11]. UA is the ultimate product of purine metabolism which is naturally found in blood in certain amounts [12]. High UA plays an important role in the pathogenesis of cardiovascular, renal disease and metabolic syndrome [13]. Meanwhile, some studies have shown that elevated UA level was related to the occurrence of hypertension [14, 15]. Elevated UA can cause reduced effectiveness of nitric oxide, endothelial dysfunction and renin angiotensin aldosterone system damage, and finally lead to vasoconstriction [16, 17]. However, the association the UA and hypertension dependence on BMI or age was unclear. We conducted a cross-sectional study to determine whether UA was significantly associated with hypertension in a sample of 4012 rural and urban communities population with overall health. In addition, we also tried to analyze the association between UA and hypertension with stratified analysis based on BMI and age.

Materials and methods

Study population and study design

The current study was a cross-sectional study to investigate the prevalence of hypertension among 24 communities in Hunan Province from 2013 to 2014. We selected 6 regions (Changsha, Zhuzhou, Hengyang, Yueyang, Xiangxi, and Yongzhou) from 14 regions in Hunan Province. Then we randomly selected two urban communities and two rural communities from each region that has been selected. The permanent residents of each survey site ≥ 30 years old were included as the targets of the survey. In this study, 5258 people should be surveyed, and 4012 people were actually surveyed, with a response rate of 76.30%. All the respondents have lived in the regions for more than 5 years. By asking about the medical history of hypertension and measuring the blood pressure of the subjects by professionals. Ultimately, a population of 4012 participants (1644 males and 2368 females) were included in our study with 1538 participants (766 males and 772 females) with hypertension. This study was approved by the Institutional Ethics Review Board of the Hunan Provincial People's Hospital, Changsha, China. Written informed consents were obtained for each subject included in this study.

Data collection

Baseline characteristics were obtained by well-trained experimental personnel using a standard questionnaire in a personal interview. Before the survey was performed, all eligible investigators were invited to attend the standard training. After resting for at least 5 min, the blood pressure of the right arm was measured using a standard mercury sphygmomanometer. Those who hid past medical history, yet with positive diagnostic result of hypertension were also set as patients with hypertension. The BMI was calculated by the weight dividing the square of the height (kg/m^2). Professionals collected fasting venous blood samples of all participants in the morning. All blood samples were centrifuged and separated on site, and sent to the Central Laboratory of Hunan Provincial People's Hospital for testing. UA, SBP, DBP, ALT, BUN, Cr, TG, TC, HDL-C, LDL-C, ApoA, ApoB, CPR, FBG and Hcy were measured by standard laboratory procedures. All general demographic information and biochemical indicators were collected following standard protocols.

Definitions

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg [18]. In subgroup analysis, we stratified age (≥ 60 years old and < 60 years old) and BMI (≥ 28 kg/m^2 and < 28 kg/m^2). Cut-off value of BMI was determined according to the Chinese definition of obesity [19]. The smoking and drinking status were also surveyed. Those who drank regularly for more than 6 months were assigned to the drinking group. Current smokers (at least one per day and consecutive cigarettes for 1 year) and former smokers were divided into current or former smokers group.

Statistical analysis

Categorical variable was expressed as number and percentage. Continuous variable was described using median and interquartile range (IR) for non-normally distributed data. Using non-parametric test for continuous variable and the χ^2 test for categorical variable to compare differences between the four groups. Univariate logistic regression was used to analyze the effects of various factors on hypertension. Stratified analysis based on BMI and age to further explore the association between UA and hypertension. SPSS 20.0 software package (SPSS, Chica, Illinois, USA) was used to perform statistical analysis and P value < 0.05 was considered statistically significant.

Results

Basic information

Subjects were 54.50 (45.00, 63.00) years old, and 40.98% were male, 38.33% were hypertension. The median (IR) value of UA was 289 (231, 362) μmol/L. The median (IR) values of UA of each group were 200 (176, 216) μmol/L, 263 (249, 280) μmol/L, 325 (308, 340) μmol/L, 417 (390, 457) μmol/L in the four groups respectively. The median (IR) value of BMI of all participants was 23.13 (20.97, 25.28) kg/m^2. There were statistically significant differences in all parameters among four groups, except for age (Table 1).

Except for TC and ApoB, other parameters were related to hypertension. Odds ratio (95% confidence interval) for the association of UA and hypertension was 2.397 (2.096, 2.740) among ≥ 60 years old comparing with among < 60 years old. Odds ratio (95% confidence interval) for the association

Table 1 Characteristics of the participants according to uric acid quartiles

	Q1	Q2	Q3	Q4	*P* value
Number	1014	997	1006	995	
Age (years old)	53.00 (44.00, 63.00)	54.00 (46.00, 62.00)	56.00 (46.00, 63.00)	55.00 (47.00, 63.00)	0.212
BMI (kg/m^2)	22.35 (20.51, 24.44)	23.02 (20.74, 25.10)	23.31 (21.48, 25.49)	23.78 (21.86, 25.97)	< 0.001
SBP (mmHg)	120.00 (110.00, 132.00)	124.00 (110.00, 140.00)	126.00 (112.00, 140.00)	126.00 (112.00, 140.00)	< 0.001
DBP (mmHg)	76.00 (70.00, 80.00)	80.00 (70.00, 86.00)	80.00 (70.00, 90.00)	80.00 (70.00, 90.00)	< 0.001
ALT (U/L)	15.00 (11.00, 22.00)	16.00 (12.00, 23.00)	18.00 (14.00, 27.00)	22.00 (17.00, 33.00)	< 0.001
BUN (mmol/L)	4.83 (3.86, 6.00)	5.00 (4.08, 6.29)	5.24 (4.26, 6.61)	5.30 (4.37, 6.47)	< 0.001
Cr (μmol/L)	73.5 (65.00, 82.00)	82.00 (74.00, 93.50)	90.00 (81.00, 102.00)	99.00 (88.00, 111.00)	< 0.001
TG (mmol/L)	1.27 (0.87, 1.81)	1.41 (0.98, 1.99)	1.52 (1.08, 2.33)	2.06 (1.33, 3.21)	< 0.001
TC (mmol/L)	4.62 (4.09, 5.18)	4.71 (4.20, 5.31)	4.82 (4.14, 5.54)	4.96 (4.46, 5.65)	< 0.001
HDL-C (mmol/L)	1.33 (1.11, 1.53)	1.28 (1.12, 1.56)	1.29 (1.11, 1.49)	1.18 (1.03, 1.44)	< 0.001
LDL-C (mmol/L)	2.56 (2.07, 3.04)	2.65 (2.19, 3.14)	2.67 (2.12, 3.24)	2.63 (2.12, 3.24)	0.018
ApoA (g/L)	1.20 (1.00, 1.30)	1.20 (1.00, 1.30)	1.20 (1.00, 1.30)	1.10 (0.90, 1.30)	< 0.001
ApoB (g/L)	0.70 (0.60, 0.90)	0.80 (0.60, 0.90)	0.70 (0.50, 0.80)	0.70 (0.50, 0.80)	< 0.001
CRP (mg/L)	5.20 (4.50, 5.85)	5.40 (4.68, 6.37)	5.32 (4.37, 6.40)	5.30 (4.60, 6.60)	< 0.001
FBG (mmol/L)	5.23 (4.75, 5.89)	5.22 (4.72, 5.98)	5.37 (4.87, 6.09)	5.50 (5.00, 6.18)	< 0.001
Hcy (μmol/L)	11.60 (9.30, 14.80)	12.50 (9.80, 15.40)	13.65 (10.90, 16.70)	14.90 (12.50, 17.20)	< 0.001
Gender, n (%)					< 0.001
Male	272 (26.82)	323 (32.40)	460 (45.73)	589 (59.20)	
Female	742 (73.18)	674 (67.60)	546 (54.27)	406 (40.80)	
Smoking history, n (%)					< 0.001
Current or former smokers	192 (18.93)	232 (23.27)	302 (30.02)	353 (35.48)	
Never smokers	822 (81.07)	765 (76.73)	704 (69.98)	642 (64.52)	
Drinking history, n (%)					< 0.001
Yes	161 (15.88)	198 (19.86)	265 (26.34)	338 (33.97)	
No	853 (84.12)	799 (80.14)	741 (73.66)	657 (66.03)	

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *ALT* Alanine aminotransferase, *BUN* Blood urea nitrogen, *Cr* Creatinine, *TG* Triglyceride, *TC* Total cholesterol, *HDL-C* High density lipoprotein cholesterol, *LDL-C* Low density lipoprotein cholesterol, *ApoA* Apolipoprotein A, *ApoB* Apolipoprotein B, *CPR* C-reactive protein, *FBG* Fasting blood glucose, *Hcy* Homocysteine

of UA and hypertension was 2.535 (2.023, 3.177) among BMI ≥ 28 kg/m^2 comparing with among BMI < 28 kg/m^2 (Table 2).

Association between uric acid and hypertension

Without adjusting any confounding factors, In univariate logistic regression, odds ratios (95% confidence intervals) for the association of UA and hypertension were 1.745 (1.440, 2.114), 2.596 (2.149, 3.135) and 2.514 (2.081, 3.038) in other three groups respectively comparing with first group. After adjusting some confounding factors (age, gender, BMI, drinking history, smoking history, ALT, BUN, Cr, TG, TC, HDL-C, LDL-C, ApoA, ApoB, CPR, FBG, Hcy), Multivariable-adjusted odds ratios (95% confidence intervals) for the association of UA and hypertension were 1.652 (1.337, 2.042), 2.187 (1.761, 2.715) and 1.740 (1.375, 2.201) in other three groups respectively comparing with first group (Table 3).

Stratified analysis

Age

In the total subjects, the research objects of < 60 years accounted for 65.60%. The research objects of 31.16% were hypertension among < 60 years old, while the research objects of 52.03% were hypertension among ≥ 60 years old. Logistic regression showed the odds ratios for the association of UA and hypertension were 1.704, 2.660 and 2.349 in other three groups comparing with first group among < 60 years old. The odds ratios for the association of UA and hypertension were 2.226, 4.340, 5.898 and 6.557 in four groups respectively among ≥ 60 years old comparing with first group among < 60 years old (Fig. 1). Simultaneously, there was an interaction between UA and age (P < 0.001).

BMI

In the total participants, the subjects of BMI < 28 kg/m^2 had 3669. The subjects of 36.39% were hypertension among BMI < 28 kg/m^2, while sujects of 59.18% were hypertension among BMI ≥ 28 kg/m^2. Logistic regression showed the odds ratios for the association of UA and hypertension were 1.659, 2.442 and 2.514 in other three groups comparing with first group among BMI < 28 kg/m^2. The odds ratios for the association of UA and hypertension were 2.170, 5.260, 5.260 and 3.730 in four groups respectively among BMI ≥ 28 kg/m^2 comparing with first group among BMI < 28 kg/m^2 (Fig. 2). Simultaneously, there was an interaction between UA and BMI (P < 0.001).

Table 2 Effects of various factors on hypertension by univariate analysis

Variables	Statistics	OR (95% CI)	*P* value
Gender			
Male	1644 (40.98%)	1	
Female	2368 (59.02%)	0.554 (0.487, 0.631)	< 0.001
Age (years old)			
< 60	2632 (65.60%)	1	
≥ 60	1380 (34.40%)	2.397 (2.096, 2.740)	< 0.001
BMI (kg/m^2)			
< 28.0	3669 (91.45%)	1	
≥ 28.0	343 (8.55%)	2.535 (2.023, 3.177)	< 0.001
Smoking history			
Current smokers	842 (21.00%)	1	
Former smokers	237 (5.90%)	1.031 (0.772, 1.376)	0.837
Never smokers	2933 (73.10%)	0.642 (0.550, 0.750)	< 0.001
Drinking history			
Yes	962 (23.98%)	1	
No	3050 (76.02%)	0.841 (0.725, 0.975)	0.022
ALT (U/L)	18.00 (13.00, 26.00)	1.010 (1.004, 1.016)	< 0.001
BUN (mmol/L)	5.12 (4.12, 6.36)	1.074 (1.036, 1.114)	< 0.001
Cr (μmol/L)	86.00 (74.00, 99.00)	1.007 (1.004, 1.010)	< 0.001
TG (mmol/L)	1.51 (1.03, 2.34)	1.178 (1.130, 1.227)	< 0.001
TC (mmol/L)	4.77 (4.20, 5.41)	1.051 (0.983, 1.123)	0.149
HDL-C (mmol/L)	1.27 (1.08, 1.51)	0.446 (0.365, 0.547)	< 0.001
LDL-C (mmol/L)	2.62 (2.12, 3.16)	0.908 (0.841, 0.981)	0.014
ApoA (g/L)	1.20 (1.00, 1.30)	0.719 (0.552, 0.938)	0.015
ApoB (g/L)	0.70 (0.50, 0.90)	1.002 (0.781, 1.286)	0.985
CRP (mg/L)	5.29 (4.55, 6.25)	1.056 (1.015, 1.099)	0.008
FBG (mmol/L)	5.33 (4.82, 6.02)	1.150 (1.102, 1.201)	< 0.001
Hcy (μmol/L)	13.2 (10.3, 16.2)	1.121 (1.102, 1.141)	< 0.001

Discussion

Few studies have explored the association between the UA and hypertension in the Chinese southern rural and urban communities population. Therefore, in this study, our

Table 3 The association between UA and hypertension in different models

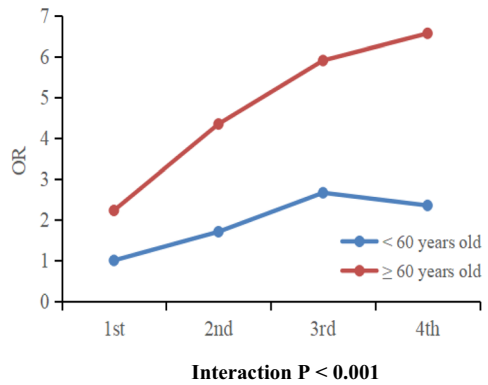
Variable	Model 1 OR (95% CI) *P*	Model 2 OR (95% CI) *P*	Model 3 OR (95% CI) *P*	Model 4 OR (95% CI) *P*
UA (μmol/L)	1.003 (1.002, 1.004) < 0.001	1.002 (1.001, 1.003) < 0.001	1.002 (1.001, 1.003) < 0.001	1.001 (1.000, 1.002) 0.002
UA (μmol/L) quartiles				
1st (≤ 231)	1	1	1	1
2nd (231–289)	1.745 (1.440, 2.114) < 0.001	1.660 (1.352, 2.039) < 0.001	1.666 (1.356, 2.046) < 0.001	1.652 (1.337, 2.042) < 0.001
3rd (289–362)	2.596 (2.149, 3.135) < 0.001	2.421 (1.977, 2.965) < 0.001	2.437 (1.989, 2.985) < 0.001	2.187 (1.761, 2.715) < 0.001
4th (> 362)	2.514 (2.081, 3.038) < 0.001	2.075 (1.687, 2.554) < 0.001	2.105 (1.710, 2.591) < 0.001	1.740 (1.375, 2.201) < 0.001

Model 1: we did not adjust any confounding factors

Model 2: we adjusted age, gender, BMI

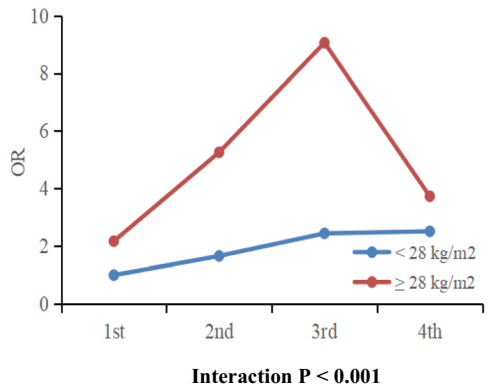
Model 3: we adjusted age, gender, BMI, drinking history, smoking history

Model 4: we adjusted for model 3 plus ALT, BUN, Cr, TG, TC, HDL-C, LDL-C, ApoA, ApoB, CPR, FBG, Hcy



UA (μmol/L) quartiles	OR (95% CI) *P* < 60 years old (n = 2632)	OR (95% CI) *P* ≥ 60 years old (n = 1380)
1st (≤231)	1	2.226 (1.662, 2.980) <0.001
2nd (231-289)	1.704 (1.324, 2.194) <0.001	4.340 (3.253, 5.790) <0.001
3rd (289-362)	2.660 (2.079, 3.404) <0.001	5.898 (4.434, 7.845) <0.001
4th (>362)	2.349 (1.831, 3.015) <0.001	6.557 (4.927, 8.727) <0.001

Fig. 1 The association between UA and hypertension after age stratification (< 60 years old, ≥ 60 years old)



UA (μmol/L) quartiles	OR (95% CI) *P* < 28 kg/m^2 (n = 3669)	OR (95% CI) *P* ≥ 28 kg/m^2 (n = 343)
1st (≤ 231)	1	2.170 (1.236, 3.808) =0.007
2nd (231-289)	1.659 (1.357, 2.029) <0.001	5.260 (3.267, 8.468) <0.001
3rd (289-362)	2.442 (2.004, 2.974) <0.001	9.056 (5.509, 14.888) <0.001
4th (> 362)	2.514 (2.060, 3.069) <0.001	3.730 (2.529, 5.550) <0.001

Fig. 2 The association between UA and hypertension after BMI stratification (< 28 kg/m^2, ≥ 28 kg/m^2)

purpose was to investigate whether the level of UA was related to hypertension in the Chinese southern population from Hunan. Simultaneously, our research also showed that UA was associated with hypertension. The association was stronger among subjects ≥ 60 years old or BMI ≥ 28 kg/m^2. To our knowledge, this was the first study to report the association between UA and hypertension in the Chinese rural and urban communities population based BMI and age stratification. Among subjects ≥ 60 years old or BMI ≥ 28 kg/m^2, the effect of UA on hypertension was stronger, and the odds ratio for the association of UA and hypertension was greater. There was an interaction between UA and age, there

was also an interaction between UA and BMI. Age and BMI may exaggerate the effect of UA on hypertension.

Previous studies have suggested that UA was associated with hypertension. The result of Kuriyama et al. showd that high uric acid (UA) level was associated with the new development of hypertension among Japanese [20]. A cohort study conducted in the United States reported that 956 people developed hypertension during the 10-years follow-up period. As the UA quartile increased, the relative risk of hypertension (95% confidence interval (CI) was dose-dependent increase (P-trend < 0.05 in all models) [21]. In a cross-sectional study of 85,286 Japanese workers, it was found that hyperuricemia was significantly associated with hypertension in different gender, which existed between men with SUA ≥ 5.3 mg/dL and women with SUA ≥ 4.3 mg/dL after adjusting for age (years), BMI, dyslipidemia (yes), diabetes (yes), and alcohol consumption (nondaily drinker), smoking (nonsmoker) and estimated glomerular filtration rate (mL/min/1.73 square meters) [22]. The review of Johnson et al. supported that UA may play a causative role in the development of hypertension, vascular disease, and kidney disease [23]. Our study also showed that UA was significantly associated with hypertension in Chinese southern rural and urban communities population, which was consistent with the results of other studies based population of different countries.

UA is produced mainly in the liver and intestines because of the high activity of xanthine oxidase (XO) in these tissues. Xanthine oxidase (XO) is an enzyme that converts hypoxanthine to xanthine and xanthine to UA [24, 25], however, oxygen free radical produced by xanthine oxidase is one of the pathogenesis of hypertension [26]. Hypoxanthine is a precursor of UA which is metabolized by XO in vascular endothelium to UA, in which reactive oxygen generated during this process inactivates NO in vascular endothelium, resulting in endothelial dysfunction [27, 28]. In addition, there are some hypotheses that UA deposits on the walls of blood vessels with activating the renin-angiotensin system, inhibiting the release of carbon monoxide and increasing inflammation, as a result, the blood vessels contract later, which leads to hypertension [29, 30]. UA can stimulate a variety of factors into vascular smooth muscle cells, causing smooth muscle cell proliferation, resulting in secondary arteriosclerosis [31]. The above are about the mechanisms that UA may affect hypertension, which provides experimental evidence for the association between UA and hypertension.

In our study, the correlation between UA and hypertension in the four groups of subjects ≥ 60 years old was stronger than that of the four groups of subjects < 60 years old respectively. Age may exaggerate the effect of UA on hypertension. The study of Norvik et al. found that an increase in the baseline level of UA can independently predict the increase in blood pressure and fasting blood glucose in overweight subjects (BMI ≥ 25 kg/m^2), but it can not predict the increase in blood pressure and fasting blood glucose in normal-weight subjects [32]. The division of BMI in our study was based on Chinese definition of obesity. The association between UA and hypertension based on BMI and age among Chinese southern rural and urban communities population needs more researches to explore and confirm.

Our research has many advantages. Firstly, this study was an observational study that included inevitable potential confusion, so we used strict statistical adjustment to minimize confusion to analyze the association between UA and hypertension by multivariate logistic regression. Secondly, this study was the first to analyze the association between the two based on BMI and age stratification among Chinese southern population from Hunan. On the other hand, there are limitations in this study. Firstly, our study was a cross-sectional study, it cannot get the causal association between UA and hypertension. Secondly, unknown confounding factors may affect the real association between the two.

Conclusions

Uric acid was significantly associated with the hypertension. The association was stronger among subjects ≥ 60 years old or BMI ≥ 28 kg/m^2.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interests.

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