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Letter to the Editor

Association between Physical Activity and Higher Serum Creatinine/Uric Acid by Dose-response Association*

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Serum creatinine (Scr) and serum uric acid (sUA) are closely related chronic disease or associated morbidity. Epidemiological evidence shows that elevated Scr or higher sUA level are independent risk factors for cardiovascular disease as well as gout and insulin resistance[1].

Physical activity (PA) is generally considered important in regulating health. Some population studies[1] have reported the association between PA and Scr. Baxmann et al.[1] recruited 170 healthy adults in Brazil and to assess PA (being classified: sedentary/moderate/high), finding that high PA increased the risk of higher Scr. However, Bharakhada et al.[2] used the same method of grouping showed that low PA is associated with a higher risk for higher Scr. Moreover, higher Scr profiles of males and females have been shown to exhibit different responses to PA[1].

Similarly, previous studies[3-4] showed that low PA is associated with higher sUA. Chen et al.[3] reported that low PA can increase the risk for high sUA, by converted PA into a categorical variable (sedentary/moderate/high). However, other studies[4-5] found that high PA increases the risk of high sUA in females using similar classification of PA.

These above inconsistent results may be caused by nonlinear association between PA and Scr/sUA. In other words, PA classification (sedentary/moderate/ high) in these studies is not a suitable method to show association of PA and Scr/sUA. Therefore, in our study, PA is classified by the dose-response relationship between PA and Scr/sUA firstly, and then to explore the relationship between PA and Scr/sUA in middle-aged individuals in China.

We used a cluster sampling method to recruit subjects from urban and rural areas in Hebei, China, between 2009 and 2011. We selected four representative urban and rural communities that met the average level of economic growth in Hebei province, a total of 4,640 subjects (1,690 males, 36.42%) were selected for analyses. This study was approved by the Ethics Committee of North China University of Science and Technology, Tangshan, China, and all participants provided written informed consent.

An organizational pretest was administered through face-to-face interviews. The first part of the survey collected essential information from all respondents, including sex, age, education, tobacco and alcohol use, frequency of food consumption, and stress from work/home/finances. The last part included the International Physical Activity Questionnaire (IPAQ)[5] to assess the PA of the respondents, which consisted of a comprehensive set of four domains: domestic and gardening activities, transportation-related activities, work-related physical activities, and leisure-time physical activities.

Higher Scr were defined as ≥ 106 μmol/L in males and ≥ 97 μmol/Lin females. Higher sUA were defined as ≥ 416 μmol/L in males and ≥ 357 μmol/L in females[6].

The mean and standard deviation (SD) were used to describe continuous variables and frequencies of categorical variables for baseline characteristics. Categorical variables were compared using the chi-squared test, and continuous variables were explored using the analysis of variance (ANOVA). Restricted cubic spline (RCS) functions[7] were used to describe the dose-response associations between PA and higher Scr/sUA adjusted for covariates which correlated with PA or

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Scr/sUA (age, sex, BMI, smoking, alcohol drinking, education, stress, fatty food intake, and vegetable/fruit intake). RCS functions were built with five knots[7] (located at the 5th, 25th, 50th, 75th, and 95th percentiles), and the group median of PA was chosen to be the reference for all spline plots (378 MET-min/week for PA). Scr and sUA were treated as continuous variables in RCS functions. Based on the results of RCS functions, we selected a PA of 600-900 MET-min/week as the reference category, depending on the number of participants with PA between 600-900 MET-min/week and the ‘U - shape’ of the RCS curve. Therefore, the subjects were divided into five groups by the same magnitude of PA (300 MET-min/week): < 300 (1,928 participants); 300-600 (1,223 participants); 600-900 (598 participants); 900-1,200 (361 participants); and > 1,200 (530 participants). Logistic regression models were applied to analyze the association of PA with higher Scr/sUA after adjusting for other relevant factors (age, sex, BMI, smoking, alcohol drinking, education, stress, fatty food intake, and vegetable/fruit intake). The strength of association was indicated by odds ratio (*OR*) and 95% confidence interval (*CI*). Dummy variables were constructed for the multi-categorical variables (tobacco use, alcohol use, and education). *P* values < 0.05 were considered statistically significant, and all statistical tests were two-tailed. All statistical analyses were conducted using SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, USA). RCS functions were built using a SAS macro presented by Desquilbet et al.[7].

A total of 4,640 participants aged 40-60 years were included in the analyses. Characteristics of the participants were showed Table S1 (available in www.besjournal.com) by PA groups.

A nonlinear association was found between higher Scr and PA (*P* for overall association = 0.001, *P* for nonlinear association < 0.001) (Figure 1). However, a linear association was found between higher sUA and PA (*P* for overall association = 0.024, *P* for nonlinear association = 0.051) (Figure 1).

Rates of higher Scr were 23.7%, 22.1%, 21.9%, 25.8%, and 34.2% in < 300, 300-600, 600-900, 900-1,200 and > 1,200 PA groups respectively. Compare to participants with 600-900 MET-min/week of PA, participants with > 1,200 MET-min/week of PA have increased risks for higher Scr after adjusting for other factors in the total population, *OR* was 1.48 (95% *CI*: 1.09, 1.93) (Table 1). These *OR*s in males was 1.69 (1.15, 2.48), respectively. The influence of PA on higher Scr has been investigated in different ethnic groups by different study methods. A population study[1] recruited 170 healthy adults to assess PA. The individuals were classified as sedentary or with mild or moderate/high PA. After adjusting for confounding factors, the results were similar to ours, namely higher PA was associated with higher Scr. However, the results of certain population studies do not concur with our findings. A cross-sectional study[2] explored the association between PA and Scr among people aged 40-75 years in the UK, and 6,749 participants were enrolled and provided consent. The participants were divided into low, moderate, and high groups based on PA. The study showed that low PA is associated with a higher risk for higher Scr. These inconsistent results were probably due to the different methods used for grouping the participants based on PA. Most above studies divided participants into two or three PA groups. The little number of groups may reduce the differences in Scr between groups, especially in a nonlinear association for PA and Scr. In our study, we can group participants depend on explicitly tendency of Scr changes with each phase of PA, the dose-response relationship shown by RCS. We also found a remarkable sex difference regarding the association

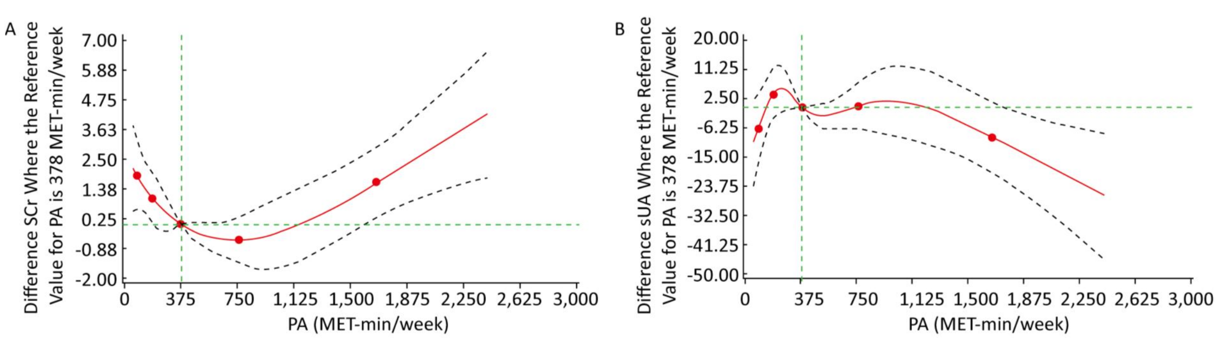

Figure 1. Association between Scr or sUA and PA using RCS with 5 knots. (A) Scr and PA. (B) sUA and PA.

between PA and higher Scr. This sex difference in association between PA and Scr is possibly because estrogens may diminish exercise-induced muscle damage, which produces Scr, leading to Scr elevation[8]. Another possible reason is that men spend more energy and are more likely to engage in vigorous activities, while women are more likely to engage in household chores and child-rearing; thus, different types of PA may entail different consequences on Scr.

Rates of higher sUA were 20.7%, 18.3%, 15.9%, 17.2%, and 18.3% in < 300, 300-600, 600-900, 900-1,200, and > 1,200 PA groups respectively Table 2. Compare to participants with 600-900 MET-min/week of PA, participants with < 300 MET-min/week of PA have increased risks for higher sUA after adjusting for other factors, *OR* (95% *CI*) was 1.32 (95% *CI*: 1.01, 1.72) in the total population. and *OR* (95% *CI*) were 1.63 (95% *CI*: 1.02, 2.60) and 1.91 (95% *CI*: 1.06, 3.44) in female participants with 300-600 and 900-1,200 MET-min/week of PA. Several studies have reported similar findings. Chen et al.[3] conducted a cohort study of 467,976 adults aged 20 years and older in Taiwan to analyze the relationship between PA and sUA, and the results showed that low PA can increase the risk for high sUA, especially in female populations. In addition, another cohort study[9] observed 330 subjects (98 men; 232 women) aged ≥ 65 years for a mean of 4.4 years in Italy. The researchers found that low PA increases the risk for higher sUA. This sex difference in association between low or moderate PA and sUA

Table 1. Association between PA and Higher Scr

Items	***OR* (95% *CI*) by PA (MET-min/week)**				
	< 300	300-600	600-900	900-1,200	> 1,200
Total					
Higher Scr	457 (23.7%)	270 (22.1%)	457 (21.9%)	93 (25.8%)	181 (34.2%)
Multivariable*	1.01 (0.79, 1.29)	1.00 (0.77, 1.30)	1	1.20 (0.85, 1.69)	1.48 (1.09, 1.93)
Males					
Higher Scr	332 (40.9%)	185 (22.8%)	83 (10.2%)	66 (8.1%)	146 (18.0%)
Multivariable*	1.15 (0.83, 1.60)	1.09 (0.76, 1.56)	1	1.27 (0.80, 1.99)	1.69 (1.15, 2.48)
Females					
Higher Scr	125 (39.1%)	85 (26.5%)	48 (15.0%)	27 (8.4%)	35 (9.4%)
Multivariable*	0.82 (0.57, 1.18)	0.87 (0.59, 1.28)	1	1.09 (0.66, 1.83)	1.19 (0.74, 1.93)

Note. *Adjusted for age, sex, body mass index, smoking, alcohol drinking, education, stress, fatty food intake, and vegetable/fruit intake. *OR*, odds ratio; *CI*, confidence interval; PA, physical activity; Scr, serum creatinine.

Table 2. Association between PA and sUA

Items	***OR* (95% *CI*) by PA (MET-min/week)**				
	< 300	300-600	600-900	900-1,200	> 1,200
Total					
Higher sUA	400 (20.7%)	224 (18.3%)	95 (15.9%)	62 (17.2%)	97 (18.3%)
Multivariable*	1.32 (1.01, 1.72)	1.24 (0.93, 1.65)	1	1.02 (0.69, 1.49)	0.93 (0.66, 1.31)
Males					
Higher sUA	278 (46.1%)	141 (23.4%)	66 (11.0%)	37 (6.1%)	81 (13.4%)
Multivariable*	1.19 (0.85, 1.68)	1.02 (0.70, 1.48)	1	0.65 (0.39, 1.06)	0.85 (0.56, 1.27)
Females					
Higher sUA	122 (44.4%)	83 (30.2%)	29 (10.6%)	26 (9.0%)	16 (5.8%)
Multivariable*	1.49 (0.95, 2.34)	1.63 1.02, 2.60)	1	1.91 (1.06, 3.44)	143 (0.54, 2.01)

Note. *Adjusted for age, sex, body mass index, smoking, alcohol drinking, education, stress, fatty food intake, and vegetable/fruit intake. *OR*, odds ratio; *CI*, confidence interval; PA, physical activity; sUA, serum uric acid.

is possibly because is that women are more likely to engage in low or moderate PA, which reduced the excretion of uric acid, because of a decreased urine volume[9]. These findings demonstrate a clear conclusion on the association of PA and sUA, low PA is associated with an increased risk for higher sUA.

The application of RCS functions to describe the dose-response association between a continuous exposure and an outcome and check the assumption of linearity of the association. Some researchers have used RCS functions to explore the risk factors for cardiovascular and kidney diseases[10]. However, it is still not a widely used method epidemiologic researches. In this study, we used a SAS macro provided by Desquilbet et al.[7] to build an RCS function for PA and higher Scr/sUA to test the nonlinear association. It is convenient to confirm the nonlinear association by graphical display. Therefore, in order to show difference between groups efficiently in epidemiologic research with large sample, we think that RCS functions could be recognized as a useful method to help grouping participants. Moreover, the SAS macro[7] is a recommendable way to build RCS functions for researchers with fewer SAS resources.

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Table S1. Characteristics of the Participants (*n* = 4,640)

Characteristics	< 300 (*n* = 1,928)	300-600 (*n* = 1,223)	600-900 (*n* = 598)	900-1,200 (*n* = 361)	> 1,200 (*n* = 530)	*P*
Age (years)	49.9 ± 5.6	49.8 ± 5.4	50.2 ± 5.2	49.4 ± 5.4	48.7 ± 5.78	0.007
BMI (kg/m^2)	24.5 ± 3.8	24.6 ± 3.9	24.5 ± 3.8	24.6 ± 3.6	24.3 ± 3.5	0.883
milk/egg/meat intake (g/day)*	112.5 (69.6, 179.9)	119.6 (67.8, 201.6)	120.6 (58.4, 194.1)	102.1 (62.8, 178.1)	89.1 (49.9, 169.0)	0.017
vegetable/fruit intake (g/day)*	457.4 (326.1, 621.1)	529.7 (343.2, 685.4)	518.1 (325.2, 678.1)	502.7 (340.4, 645.2)	492.1 (317.2, 677.9)	0.110
GLU (mmol/L)	5.3 ± 0.5	5.3 ± 0.5	5.3 ± 0.5	5.4 ± 0.5	5.3 ± 0.5	0.108
Sex (*n*, %)						< 0.001
Male	701 (36.4)	401 (32.8)	193 (32.3)	135 (37.4)	260 (49.1)	
Alcohol use (*n*, %)						< 0.001
Never	29 (1.5)	19 (1.6)	6 (1.0)	2 (0.5)	6 (1.1)	
Formerly	365 (19.4)	218 (18.1)	128 (21.6)	77 (21.4)	168 (32.1)	
Current	1,486 (79.1)	965 (80.3)	459 (77.4)	281 (78.1)	350 (66.8)	
Tobacco use (*n*, %)						< 0.001
Never	1,358 (72.8)	880 (74.1)	446 (76)	261 (73.5)	302 (58.0)	
Formerly	44 (2.4)	31 (2.6)	18 (3.0)	8 (2.2)	18 (3.5)	
Current	464 (24.8)	277 (23.3)	123 (21.0)	86 (24.3)	200 (38.5)	
Education (*n*, %)						0.016
Primary	492 (25.6)	263 (21.6)	131 (22.0)	83 (23.1)	132 (25.0)	
Secondary	1,353 (70.4)	896 (73.4)	437 (73.6)	265 (73.8)	387 (73.3)	
Senior	76 (4.0)	61 (5.0)	26 (4.4)	11 (3.1)	9 (1.7)	
Stress (*n*, %)						< 0.001
Yes	1,147 (59.5)	749 (61.2)	372 (13.6)	208 (62.2)	258 (49.7)	

Note. *Median (Q1, Q3) and *P* for a nonparametric test. PA, physical activity; BMI, body mass index; GLU, glucose; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CHO, cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.