No associations exists between red blood cell distribution width and serum uric acid in both sexes

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Abstract
The aim of this study was to determine whether there was a significant association between red blood cell distribution width (RDW) and uric acid (UA) in a large Chinese population.

This was a cross-sectional study with an enrollment of 80,298 ostensibly healthy participants (48,971 males, 31,327 females) during the period from 2011 to 2015. In the study, database was grouped by sex and the association between RDW and UA was analyzed by quartiles of RDW.

UA values between different sexes and RDW subgroups were analyzed by 2-way analysis of variance and Bonferroni t tests. Prevalence of hyperuricemia in different sexes was calculated. The relationship between risks of hyperuricemia and RDW level was analyzed by binary logistic regression with or without adjustment for age and body mass index.

UA values were not all the same between different sexes and RDW subgroups. Males had significantly higher hyperuricemia prevalence than females (20.00% vs 6.48%, P < .01). In addition, hyperuricemia prevalence in males decreased slightly across RDW quartiles, but was stable in females. No significant association between hyperuricemia risk and RDW was found in both sexes according to the results of multivariate logistic regression analysis. Similarly, negative results were also observed in multivariate linear analysis when both RDW and UA were considered as continuous variable.

We could not find any significant relationship between RDW and UA in both sexes.

Abbreviations: ALT = alanine aminotransferase, ANOVA = analysis of variance, BMI = body mass index, CRP = C-reactive protein, CVD = cardiovascular diseases, ESR = erythrocyte sedimentation rate, LDL = low-density lipoprotein, MCV = mean corpuscular volume, MS = metabolic syndrome, OR = odd ratio, RBC = red blood cell, RDW = red blood cell distribution width, TG = triglycerides, UA = uric acid, WBC = white blood cell.

Keywords: red blood cell distribution width, uric acid, gender, age

1. Introduction
Red blood cell distribution width (RDW) is an erythrocyte parameter, which is calculated by dividing the standard deviation of erythrocyte volume with erythrocyte mean corpuscular volume (MCV) and then multiplying by 100. RDW has traditionally been used for the differential diagnosis of anemia.[1] In recent years, several studies have demonstrated that increased RDW is associated with a poor prognosis in clinical settings of cardiovascular and thrombotic diseases,[2] stroke,[3] coronary artery disease,[4] diabetes mellitus,[5] hypertension,[6] metabolic syndrome (MS),[7,8] renal function damage,[5,9] and it can be a predictor of all-cause mortality in general population.[2] However, it has not been well ascertained whether anisocytosis might be a cause or a simple epiphenomenon of the underlying conditions of the above-mentioned diseases, such as inflammation, oxidative stress, under nutrition, and so forth or maybe an element of both.[10]

Uric acid (UA) is the final metabolism product of endogenous and exogenous purine nucleotide.[10,11] Approximately 70% of UA is excreted in the kidney while the remaining part is excreted by the intestinal tract.[12] Higher concentration of UA leads to development of hyperuricemia and gout. Elevated serum UA is also suggested to be associated with type 2 diabetes,[13] hypertension,[14] cardiovascular diseases (CVD),[15,16] thyroid dysfunction,[17] and MS.[18]
From above description, we can see that both RDW and UA have correlations with multiple diseases, so we want to explore whether a correlation exists between RDW and UA that seems irrelevant. There was only 1 publication we could retrieve which focused on the relationship between RDW and UA. Luo et al. [19] found that RDW was independently correlated with UA after adjustments of several related factors in 512 patients with newly diagnosed hypertension without treatment. This earlier research had limitations in several aspects, such as small sample size, recruiting only patients with hypertension, and so forth. In fact, taken into account of the above-mentioned characteristics of RDW and UA, we want to explore whether a relationship between RDW and UA exists in healthy people rather than in people who suffer from any particular diseases, emphasizing on different genders with large sample size. Therefore, the goal of present study was to systematically evaluate the association between RDW and UA in a large number of Chinese individuals. Special attention was paid to the gender differences.

2. Materials and methods

2.1. Design
This study was based on a cross-sectional, community-based health check investigation, which was initiated nearly 5 years ago, and conducted in Tianjin Medical University General Hospital. The Departments of Health Management, Endocrinology and Metabolism, and Nuclear Medicine collaborated in this research. The protocol was developed and executed as previously by our group in accordance with the Declaration of Helsinki. [17, 19] For the current analysis, all subjects were self-reported as healthy without any known previous diseases. All participants were asked to complete a questionnaire about medical history, lifestyle, and alcohol intake and then provide an overnight fasting blood sample. All participants were healthy as they reported. To avoid the influence of confounding factors, the exclusion criteria were subjects with disease history of blood disease; subjects with any diseases or taking any medicine that might affect UA; subjects with a history of cardiac diseases, kidney diseases, and liver diseases. All participants were required to receive a questionnaire inquiries. During the period from 2011 to 2015, a total of 80,298 candidates (48,971 males, 31,327 females) with complete data for analysis were finally included in this particular subject.

2.2. Ethics
The institutional review board and ethic committee of Tianjin Medical University General Hospital approved the ethical, methodological, and protocol aspects of this investigation. We confirm that all methods in the current study were carried out in accordance with the relevant guidelines and regulations. All participants in this research provided their informed consents, so every people participated in our study voluntarily and comprehended all aspects about the research.

2.3. Measurements
Anthropometric examinations and fasting blood sample tests of participants were performed when participants visited our institution. Height, waist, and weight were measured in centimeters and kilograms, respectively. Body mass index (BMI) was calculated by dividing body weight (kg) by the square of body height (m²). Blood pressure was measured with a standard mercury sphygmomanometer after a sedentary for at least 5 minutes. Alanine aminotransferase (ALT), total bilirubin, blood urea nitrogen, creatinine, UA, total cholesterol, triglycerides (TG), high-density lipoprotein, low-density lipoprotein (LDL), and glucose were determined enzymatically by an autoanalyzer (Hitachi Corporation, Tokyo, Japan). C-reactive protein (CRP) was done on an analyzer (Hebei Diagnostics, Shijiazhuang, China), and erythrocyte sedimentation rate (ESR) was determined by Wintergreen’s method (Yakun Diagnostics, Tianjin, China). White blood cell (WBC), granulocyte, lymphocyte, red blood cell (RBC), hemoglobin, RDW, RBC specific volume, MCV, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet, platelet distribution width, and mean platelet volume were measured with a hemocytometer analyzer (Sysmex Corporation, Kobe, Japan).

2.4. Definition
The diagnosis of hyperuricemia required a UA level of >420 μmol/L for males and >360 μmol/L for females. [17, 18] The grouping method for RDW was based on quartiles of the measurements.

2.5. Statistical analysis
In order to see if there exist any differences in different intervals, RDW was grouped based on quartiles rather than continuous variable. UA values were presented as mean ± standard deviation, 2-way analysis of variance (ANOVA) and Bonferroni post hoc test were accomplished to analyze differences of UA between different RDW quartiles and sexes. Chi-squared test was applied to compare hyperuricemia prevalence differences between subgroups. The binary logistic regression models were made to calculate the crude odds ratio (OR) for hyperuricemia with 95% confidence intervals by stratifying data with RDW quartiles. In the last, the correlation between UA and RDW was explored by univariate and multiple linear regression analyses. Backward method was used for variable selection in the multiple linear regression analyses. Statistical analysis was conducted by the Statistical Package for Social Sciences (SPSS version 17.0, Chicago, IL) and P < .05 was regarded as significance.

3. Results

3.1. UA values between different sexes and RDW subgroups
In Table 1, 2-way ANOVA results showed the statistics for sex was F = 37,472.017 (P < .01), and for RDW subgroups was F = 17,525 (P < .01). For interaction of sex × RDW subgroups was F = 6,240 (P < .01). Further Bonferroni post hoc test demonstrated the significant differences in UA between subgroups of RDW ≤ 12.2 and 12.2 < RDW ≤ 12.6, 12.6 < RDW ≤ 13.0, RDW > 13.0, and the differences between 12.6 < RDW ≤ 13.0 and RDW > 13.0 subgroups (P < .05).

3.2. Prevalence of hyperuricemia in different genders
The prevalence of hyperuricemia in this population was 14.76% (11,855/80,298). Males had significantly higher hyperuricemia prevalence than females (Table 2). All RDW quartiles demon-
Chi-squared value

In our study, we used binary logistic regression models to analyze the risks of developing hyperuricemia in relation to different variables. OR calculation was performed with highest quartile of RDW as reference (Table 3), and other risk factors included age and BMI were adjusted. We could not identify significant risks after adjustment with covariates for hyperuricemia in both males and females, suggesting covariates greatly influenced the relationship between RDW and UA.

From Table 4, we concluded that BMI, ALT, and TG display detrimental effects to develop hyperuricemia in both sexes while the effect of age in the opposite sex. When RDW is viewed as continuous variable, the relations of RDW and CRP to hyperuricemia were consistent with the previous results.

### 3.4. Relationship between UA and RDW by univariate and multiple linear analyses

Univariate linear analyses were used first to demonstrate any association between UA versus RDW, age, BMI, and all other factors (Table 5). We found that the correlation between UA and RDW existed in male but not in female, besides, we did not find significant relationship between UA and ESR in both genders. Multiple linear regression models were further performed, and the variables which were significant in the univariate analysis were considered as covariates. The insignificance of RDW retained according to the result of multiple linear regression. In general, no relationship between UA and RDW could be rendered in both males and females (Table 6).

### 4. Discussion

The current investigation demonstrates that in healthy population, males have significantly higher hyperuricemia prevalence than females. Hyperuricemia prevalence in males decreases slightly across RDW quartiles, but was stable in females. More importantly, this is the first study that demonstrated no association existed between RDW and UA in healthy people without any diseases in either gender, indicating that covariates could greatly confound the relationship between RDW and UA.

RDW is a parameter derived from routine blood cell counts, which can be automatically calculated from MCV by hematology analyzers. RDW reflects the degree of heterogeneity in size of the peripheral erythrocytes. There are many factors can affect RDW value, which include iron, vitamin B12, folic acid, erythropoietin, and so forth. An increased RDW suggests a profound deregulation of erythrocyte homeostasis including both impaired erythropoiesis and abnormal erythrocyte metabolism. And elevated RDW is accompanied by lower erythrocyte deformability.

There are elevating numbers of researches evaluating diagnostic and prognostic values of RDW in diseases besides hematology. However, apparent contradictions exist. In CVD, for instance, a review demonstrated that a higher level of RDW was associated with adverse outcomes in patients with or without CVD even after adjusting with several confounding variables. The authors concluded that the states of oxidative stress and inflammation might be important determinants of RDW. As such, Marinkovic et al suggested that oxidative stress could shorten erythrocytes' lifespan and make them prone to be hemolytic. Inflammatory cytokines, such as tumor necrosis factor α and interleukin, are strongly related to ineffective erythropoiesis by desensitizing bone marrow erythroid progenitors to erythropoietin, inhibiting RBC maturation, and thereby promoting anisocytosis. Nevertheless, in another study, no association was found between RDW concentrations and all-cause mortality in non-ST elevation myocardial infarction patients although a positive association between high levels of RDW and the severity of coronary artery disease was shown. And the relationship between RDW and CRP was yet to be clarified. Likewise, another investigation conducted by Yoon et al elucidated that baseline RDW was not associated with adverse outcomes in 337 CVD patients with end-stage renal diseases treated by dialysis. It did not clearly demonstrate whether

### Table 2

Incidence (and case number count) in different red blood cell distribution width quartiles and genders.

| Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | Total |
|------------|------------|------------|------------|-------|
| Males      |            |            |            |       |
| Normouricemia | 9648 (79.17%) | 10,027 (79.23%) | 9327 (80.27%) | 10,145 (81.10%) | 39,147 (79.94%) |
| Hyperuricemia | 2538 (20.83%) | 2629 (20.77%) | 2292 (19.73%) | 2365 (18.90%) | 9824 (20.00%) |
| Females    |            |            |            |       |
| Normouricemia | 8778 (93.46%) | 7706 (93.84%) | 6310 (93.34%) | 6502 (93.38%) | 29,296 (93.52%) |
| Hyperuricemia | 614 (6.54%) | 506 (6.16%) | 450 (6.66%) | 461 (6.62%) | 2031 (6.48%) |

Hyperuricemia defined as >420 μmol/L in males and >360 μmol/L in females.

1. Comparing the incidence of hyperuricemia between males and females by chi-squared method.

2. P < 0.01.

**Table 1**

Uric acid values between different sexes and red blood cell distribution width subgroups.

| RDW subgroups | Total     | Male      | Female    |
|---------------|-----------|-----------|-----------|
| RDW ≤ 12.2   | 321.74±84.167 | 365.11±74.214 | 265.47±59.355 |
| 12.2 < RDW ≤ 12.6 | 325.23±84.497 | 364.50±74.760 | 264.69±59.062 |
| 12.6 < RDW ≤ 13.0 | 326.03±82.931 | 361.26±73.788 | 265.47±59.496 |
| 13.0 < RDW     | 324.04±84.477 | 358.02±75.917 | 263.00±61.670 |

Analyzed by 2-way analysis of variance. RDW = red blood cell distribution width.
controls. This study proposed that gene polymorphisms and deletions might assume the main responsibility in regulating variations existed because of the following points. First, only 512 middle-aged hypertensive participants without antihypertensive treatment were recruited in the previous study, but the present study focused on the relationship between RDW and UA and the largest sample size until now, and our participants were generally different from our research. We considered that gene polymorphisms were suggested to be related with a high level of UA concentration. Adiposity, weight gain, hypertension, and diuretics have been considered as risk factors for gout in men, while weight loss is protective. Second, Hamur et al suggested that elevation in serum UA level contributed to oxidative stress, endothelial dysfunction, and smooth muscle cell proliferation. UA functions as an antioxidant in the presence of native LDL taken from human plasma, but in response to mildly oxidized LDL, UA becomes a pro-oxidant. UA also plays a pro-oxidant role in the process of adverse outcomes. Third, genetic factors are considered important for gout development. In fact, homozygous deleterious mutation and polymorphisms in the SLC22A12 gene was suggested to be related with a high level of UA and gout in a study. Another study elucidated that C677T mutation in methylene tetrahydrofolate reductase gene was a risk factor of hyperuricemia in elderly Korean men. Among different genotypes (GG, GT, and TT), different UA levels were shown. On the other hand, there are also many influential factors for RDW (e.g., measuring technique, age, gender), which should be considered when interpreting the results. A study conducted by Gunawardena et al elucidated that RDW value could changed significantly from 24 hours of storage at different temperatures. Lippi et al demonstrated that different analyzers showed broad variation of RDW values in the same blood.

| Hyperuricemia | Parameter values | Crude OR (CI) | Adjusted OR (CI) |
|---------------|-----------------|---------------|-----------------|
| RDW quartile 4 | RDW > 13.10 (reference) | | |
| RDW quartile 3 | 12.60 < RDW ≤ 13.10 | 1.061 (0.994–1.132) | 0.997 (0.933–1.066) |
| RDW quartile 2 | 12.30 < RDW ≤ 12.60 | 1.128 (1.053–1.210) | 1.044 (0.972–1.122) |
| RDW quartile 1 | RDW ≤ 12.30 | 1.142 (1.072–1.216) | 1.025 (0.960–1.095) |

CI = confidence interval, OR = odds ratio, RDW = red blood cell distribution width.

Table 3
The risks of hyperuricemia according to red blood cell distribution width quartiles in different genders.

### Table 4
The likelihood of developing hyperuricemia in different variables.

| Variables | OR (CI) | P | OR (CI) | P |
|-----------|---------|---|---------|---|
| Age       | 0.992 (0.9870–0.997) | .002 * | 1.021 (1.010–1.031) | .000 ** |
| BMI       | 1.121 (1.102–1.140) | .000 ** | 1.153 (1.117–1.189) | .000 ** |
| ALT       | 1.013 (1.009–1.016) | .000 ** | 1.019 (1.010–1.027) | .000 ** |
| RDW       | 1.071 (1.079–1.170) | .133 | 0.956 (0.791–1.154) | .637 |
| CRP       | 1.009 (0.981–1.037) | .541 | 1.091 (0.995–1.197) | .063 |
| TG        | 1.251 (1.208–1.296) | .000 ** | 1.272 (1.166–1.389) | .000 ** |

ALT = alanine aminotransferase, BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, OR = odds ratio, RDW = red blood cell distribution width, TG = triglycerides.

* P < .05.
** P < .01.
The present study has several shortcomings. First, the relationship cannot be confirmed because of the nature of this cross-sectional study. Further prospective and interventional studies are necessary to explain the question. Second, inflammatory cytokines (such as interleukin and tumor necrosis factor α) were not measured in this investigation due to budget shortage. Third, we checked blood parameters only on a single blood sampling, but we did not double check due to budget shortage. This may be less precise than repeated measurements. And finally, detailed food recall and some other consumed drugs, which could influence hematological parameters or metabolism, should be recorded in specific details for risk stratification in further research.

In conclusion, we found no significant relationship between RDW and UA in both sexes in the current study. There are many factors that affect RDW and UA, so the changes of RDW and UA might only be an epiphenomenon. There was little research for the relationship between RDW and UA and we can only make a conclusion that no relationships exist between RDW and UA in this study, we want to examine the cofounders and mediators for the relationship in future study.

Acknowledgments
The authors thank Professor Yaguang Fan (a dedicated statistician from Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital, Tianjin, China) for reviewing statistical analyses of the paper.

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Table 5
Relationship between uric acid and different variables by univariate linear analyses.

| Sex  | Variables | R   | P     | R   | P     |
|------|-----------|-----|-------|-----|-------|
|      |           | Males |       | Females |       |
| Age  | 0.094     | .000** | 0.222 | .000** | |
| BMI  | 0.252     | .000** | 0.329 | .000** | |
| SBP  | 0.070     | .000*  | 0.241 | .000** | |
| DBP  | 0.112     | .000** | 0.176 | .000   | |
| ALT  | 0.208     | .000** | 0.201 | .000   | |
| Cr   | 0.248     | .000** | 0.309 | .000** | |
| TC   | 0.135     | .000** | 0.202 | .000** | |
| TG   | 0.238     | .000** | 0.287 | .000** | |
| LDL  | 0.163     | .000** | 0.207 | .000** | |
| HDL  | 0.091     | .000** | 0.127 | .000   | |
| GLU  | 0.075     | .000*  | 0.085 | .000   | |
| CRP  | 0.017     | .000   | 0.013 | .000   | |
| ESR  | 0.005     | .349   | 0.141 | .000** | |
| WBC  | 0.082     | .000** | 0.115 | .000   | |
| RBC  | 0.081     | .000** | 0.010 | .079   | |
| RDW  | 0.015     | .01   | 0.016 | .01   | |

ALT = alanine aminotransferase, BMI = body mass index, Cr = creatinine, CRP = C-reactive protein, DBP = diastolic blood pressure, ESR = erythrocyte sedimentation rate, GLU = glucose, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RBC = red blood cell, RDW = red blood cell distribution width, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, WBC = white blood cell.

Table 6
Relationship between uric acid and red blood cell distribution width by multiple linear analyses.

| Sex  | Variables | B   | P     | B   | P     |
|------|-----------|-----|-------|-----|-------|
|      |           | Males |       | Females |       |
| Age  | 38.761    | .000** | 192.534 | .000** | |
| BMI  | -0.018    | .244   | -0.602 | .000   | |
| SBP  | 0.578     | .000** | 4.156  | .000** | |
| DBP  | -0.267    | .000** | 0.296  | .000** | |
| ALT  | 0.527     | .000** | 0.422  | .000** | |
| Cr   | 1.582     | .000** | 1.422  | .000   | |
| TC   | 22.520    | .000   | 25.912 | .000   | |
| TL   | 0.029     | .209   | 6.072  | .000   | |
| HDL  | -0.208    | .000** | 24.763 | .000   | |
| LDL  | -16.062   | .000** | 11.124 | .000   | |
| GLU  | -0.017    | .176   | -7.422 | .000** | |
| WBC  | 3.265     | .857   | -0.002 | .851   | |
| RBC  | -11.253   | .000   | 11.124 | .000   | |
| RDW  | -0.013    | .304   | 0.006  | .562   | |
| CRP  | 2.222     | .007** | 0.986  | .20    | |

ALT = alanine aminotransferase, BMI = body mass index, Cr = creatinine, CRP = C-reactive protein, DBP = diastolic blood pressure, ESR = erythrocyte sedimentation rate, GLU = glucose, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RBC = red blood cell, RDW = red blood cell distribution width, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, WBC = white blood cell.

* P < .05.
** P < .01.
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