BMJ Open

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-019792 |
| Article Type: | Research |
| Date Submitted by the Author: | 26-Sep-2017 |
| Complete List of Authors: | Huang, LingLing<br>Dou, Dong-Mei; Henan University, Public Health, School of Nursing<br>Liu, Nan; Guangzhou Medical University, School of Public Health<br>Wang, XiaoXiao; Henan University, Public Health, School of Nursing<br>Fu, Li-Ying; Henan University, Public Health, School of Nursing<br>Wu, Xiao; Henan University, Public Health, School of Nursing<br>wang, peixi; Department of Preventive Medicine, School of Public Health, Guangzhou Medical University, |
| Primary Subject Heading: | Cardiovascular medicine |
| Secondary Subject Heading: | Public health, Epidemiology |
| Keywords: | Erythrocyte parameters, Metabolic syndrome, Pearl River Delta region, China |
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# Association of erythrocyte parameters with metabolic syndrome in the Pearl River Delta region of China

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**Abstract**

**Objective:** Increasing studies have reported that erythrocyte parameters, including red blood cell (RBC), hematocrit (HCT), hemoglobin (Hb), and red blood cell distribution width (RDW), are associated with metabolic syndrome (MetS) in adults worldwide. However, the association, stratified by sex, in populations in the Pearl River Delta region of China remains to be elucidated. Therefore, our aim was to explore the association of erythrocyte parameters with MetS, stratified by sex in the Pearl River Delta region of China.

**Methods:** In this cross-sectional study, 2161 males and 2511 females were enrolled. MetS was diagnosed using a modified version of the Adult Treatment Panel III (ATP III) criteria. Logistic regression analyses were performed to calculate adjusted odds ratios (ORs) of erythrocyte parameters associated with MetS stratified by sex.

**Results:** The prevalence of MetS was higher in females than that in males (35.2% vs. 26.7%). RBC, HCT, Hb and RDW values increased linearly with the number of MetS components from zero to five identified in both males and females. Among males, the ORs of MetS risk increased across the tertiles of Hb (Q2: OR=1.687, 95% confidence interval [CI]=1.151~2.472; Q3: OR=2.252, 95%CI= 1.550~3.272 ). Males in the highest tertiles of RDW had a 2.750-fold increased risk of suffering from MetS compared to those in the reference group. Among females, the ORs of MetS risk increased across

the tertiles of HCT (Q2: OR=1.738, 95%CI=1.229~2.458; Q3: OR=1.922, 95%CI=1.337~2.761). Females in the highest tertiles of RBC had a 1.785-fold increased risk of experiencing MetS compared to those in the reference group.

**Conclusions:** MetS was more prevalent in females than that in males. The association between erythrocyte parameters and MetS differed between sex, whereby RBC and HCT were identified as the risk factors of MetS in females and Hb and RDW as the risk factors in males.

**Keywords:** Erythrocyte parameters, Metabolic syndrome, Pearl River Delta region, China



**Strengths and limitations of this study**

- The large sample of subjects was enrolled in our survey.
- This is the first study to explore the the association of erythrocyte parameters with MetS, stratified by sex in the Pearl River Delta region of China.
- The present study was designed as a cross-sectional study; therefore, direct causation cannot be concluded from the results.
- Supplementary information about the lifestyle of the subjects was not collected; therefore, these factors could not be included in the adjustments of our multivariate logistic regression analyses.

**Introduction**

Metabolic syndrome (MetS) is defined as a cluster of multiple correlated metabolic features, including abdominal obesity, hypertension, elevated triglyceride (TG) levels, decreased high-density lipoprotein cholesterol (HDL-C) levels, and hyperglycemia.[1]. It is known to be strongly associated with an increased risk of type 2 diabetes [2], cardiovascular disease (CVD) [2-4], and all-cause mortality [4]. In recent years, MetS has emerged as a global public health issue owing to its increased prevalence around the world, affecting nearly 20-30% of adults in many countries [5-7]. Hence, early identification of individuals at high risk of MetS is essential for the prevention of MetS.

Currently, the pathogenesis of MetS is not clearly understood. Generally, MetS is often accompanied by insulin resistance and/or chronic low-grade inflammation [8-9]. Numerous investigators previously reported that erythrocyte parameters levels, including red blood cell (RBC), hematocrit (HCT), hemoglobin (Hb) and red blood cell distribution width (RDW) were positively associated with a insulin resistance and chronic low grade inflammation [10-14]. In fact, RBC [14-16], HCT [15-16], Hb [14-15, 17] and RDW[18] were demonstrated in several studies worldwide to correlate with MetS in adults. However, the association between erythrocyte parameters and MetS remains controversial, because the results reported are inconsistent depending on the different ethnic population studied. In addition, discrepancies in the results may be partly attributed to the sexes differences. Many studies simply applied sex as an adjustment variable to investigate the relationship between erythrocyte parameters and MetS, and no studies were conducted in the Pearl River Delta region of China. Therefore, the aim of this study was to explore the association between erythrocyte parameters and MetS stratified by sex in the Pearl River Delta region of China.



## Materials and Methods

### Study participants

This cross-sectional study involved participants who underwent a general health examination at the Community Health Service Agencies in the Pearl River Delta region of China in 2015. The health examination included recording of medical history, anthropometric measurements, and laboratory tests.

Participants with a history of cardiovascular diseases, severe liver and kidney dysfunction, tumors, and severe inflammatory diseases were excluded. In addition, we excluded participants who did not have complete data on their MetS components and erythrocyte parameters. Altogether, a total of 4672 subjects (2161 males and 2511 females) were enrolled in this study. The study was approved by the Ethics Committee of Guangdong Sociological Society. Written informed consent was obtained from all participants.

**Data collection and measurements**

The medical history of subjects was obtained by review of self-reported questionnaires. Anthropometric parameters were measured by trained staff, following a standardized protocol. Height, weight, waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured in replicate, and mean values were calculated for this study. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. After an overnight fast, venous blood samples from participants were obtained to measure blood levels of routine laboratory tests, including TG, total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), uric acid (UA), white blood cell (WBC), platelet (PLT), RBC, HCT, Hb, RDW, alanine transaminase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase;(GGT), albumin (ALB) and glycated hemoglobin A1c (HbAIc).

**Tertiles of erythrocyte parameters levels**

Erythrocyte parameters levels were categorized into tertiles on the basis of the individual distributions for males and females, respectively (in males: RBC, Q1<4.37 × $10^{12}$/L, Q2=4.37~4,75 × $10^{12}$/L, Q3≥ 4.76 × $10^{12}$/L; HCT, Q1<39.8%, Q2=39.8~42.4%, Q3≥42.5%; Hb, Q1<137 g/L, Q2=137~146 g/L, Q3 ≥147 g/L; RDW, Q1<12.5%, Q2=12.5~13.1%, Q3≥13.2%; in females: RBC, Q1<3.96 × $10^{12}$/L, Q2=3.96~4,27 × $10^{12}$/L, Q3≥4.28 × $10^{12}$/L; HCT, Q1<35.2%, Q2=35.2~37.3%, Q3≥37.4%; Hb, Q1<120 g/L, Q2=120~127 g/L, Q3≥128 g/L; RDW, Q1<12.3%, Q2=12.3~12.8%, Q3≥12.9%).

**Definition of metabolic syndrome**

MetS was diagnosed using a modified version of the Adult Treatment Panel III (ATP III) criteria [1], which included at least three of the following five components: 1) WC≥90 cm in males and WC≥80 cm

in females; 2) SBP≥130 mmHg or DBP≥85 mmHg; 3) TG≥1.70 mmol/L; 4) HDL-C<1.03 mmol/L in males and HDL-C<1.29 mmol/L in females; and 5) FPG≥5.6 mmol/L.

**Statistical analysis**

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago,IL, USA). Data were presented as the mean ± standard deviation or frequency (percentage). The *t*-test was used to evaluate the differences in characteristics of study subjects with and without MetS stratified by sex. The $X^2$ test was performed to compare the proportion of MetS components, from zero to five, between males and females, and compare the prevalence of MetS dependent on the tertiles of RBC, HCT, Hb, and RDW between males and females, respectively. The one-way ANOVA was conducted to test mean levels of erythrocyte parameters according to the number of MetS components in males and females, separately. Multivariate logistic regression analyses were performed to calculate adjusted odds ratios (ORs) of erythrocyte parameters associated with MetS stratified by sex. *P* value <0.05 was considered to be statistically significant.

**Results**

**Prevalence of MetS**

In total, there were 2161 males and 2511 females enrolled in this study. Of the subjects, 576 males (26.7%) and 885 females (35.2%) were diagnosed with MetS.

**Characteristics of study subjects**

In this study, among the males, the mean age of the MetS group was significantly lower than that of the non-MetS group, whereas the opposite trend was observed among the females ($P$<0.001). In the cluster of MetS components, WC, SBP, DBP, TG, and FPG levels were remarkably greater in the MetS group than in the non-MetS group among both males and females, but HDL-C levels were significantly lower in the MetS group than that in the non-MetS group among both males and females ($P$<0.001). In the cluster of erythrocyte parameters, we found that RBC, HCT, Hb and RDW were significantly higher in

the MetS group than that in the non-MetS group among both males and females ($P$<0.001). Additional information about the characteristics of study subjects with and without MetS stratified by sex are presented in Table 1.

**Proportion of MetS components**

Our results revealed that most males experienced one metabolic disorder, and most females suffered from two metabolic disorders. In addition, the proportion of MetS components from two to five was significantly lower in males than that in females (25.5% vs. 27.8%, 18% vs. 21.3%, 7.5% vs. 11.3%, 1.1% vs. 2.6, respectively). Additional information is shown in Fig 1.

**Association of erythrocyte parameters with MetS**

This study showed that the levels of RBC, HCT, Hb and RDW levels clearly increased with the number of MetS components from zero to five identified in both males and females ($P$<0.001, shown in Table 2), Figure 2 showed that the prevalence of MetS increased in a dose-dependent manner as the tertiles of RBC, HCT, Hb and RDW levels increased in both males and females, Furthermore, at each tertiles of RBC, HCT, Hb and RDW levels, the prevalence of MetS was lower in males than that in females, except at the highest tertiles of RDW levels (shown in Fig 2).

**Logistic regression analysis model**

The adjusted ORs of MetS risk associated with each tertile of RBC, HCT, Hb, and RDW are listed in Table 3. After adjusting for potential confounders, the significant association of Hb and RDW with MetS was observed in males, but this was not true for RBC and HCT. The ORs of MetS risk increased across the tertiles of Hb in males (Q2: OR=1.687, 95% confidence interval [CI]=1.151~2.472; Q3: OR=2.252, 95%CI= 1.550~3.272 ). Males in the highest tertiles of RDW had a 2,750-fold increased risk of suffering from MetS in comparison to those in the reference group. Only RBC and HCT levels were observed to associate with MetS in females. The ORs of MetS risk increased across the tertiles of HCT(Q2: OR=1.738, 95% CI=1.229~2.458; Q3: OR=1.922, 95%CI=1.337~2.761). Female in the highest tertiles of RBC had a 1.785-fold increased risk of experiencing MetS in comparison to those in the reference group.

## Discussion

### Main findings

The prevalence of MetS was higher in females than that in males (35.2% vs. 26.7%). The levels of RBC, HCT, and Hb and RDW increased linearly with the number of MetS components from zero to five identified in both males and females. The association between erythrocyte parameters and MetS differed between sexes, whereby Hb and RDW were identified as the risk factors of MetS in males and RBC and HCT as the risk factors in females.

### Comparisons with Previous Studies

Sex has been demonstrated as an important factor in the prediction of MetS development. Several previous studies have showed that females have a higher prevalence of MetS than males [19-20]. A large-scale study conducted in Russia reported that the prevalence of MetS diagnosed using the ATP III criteria, was 9.5% in men and 23.5% in women [19]; A study performed in the seven geographical regions of Turkey showed that the prevalence of MetS as determined by the ATP III criteria, was 28% in men and 39.6% in women [20]. The present study confirmed that the prevalence of MetS was, in fact, higher in females (35.2%) than in males (26.7%). Additionally, it was observed that the mean age of the MetS group in females was higher than that of the MetS group in males (59.78 ± 12.34 years vs. 51.39 ± 12.21 years). We hypothesized that the difference observed in the prevalence of MetS between females and males could be attributed to this age difference. It has been well established that the prevalence of MetS significantly increases with age [20-21].

It is well known that MetS represents a cluster of simultaneously occurring metabolic abnormalities. In fact, previous studies demonstrated that RBC and Hb levels clearly increased in a line fashion with the numbers of MetS components [16. 22]. Our findings were consistent with those of these reports. Moreover, our results showed that HCT and RDW were demonstrated a similar trend in relation to the number of MetS components. It has been shown that a higher number of MetS components is associated with insulin resistance. Several studies demonstrated that levels of RBC, HCT and Hb were significantly associated with insulin resistance [10, 12, 23]. We hypothesized that

the increased levels of the tested erythrocyte parameters in this study may be indicative of the development of insulin resistance.

Many studies have demonstrated the association between RBC levels and MetS, implicating RBC as a potential hematological marker for early detection of MetS [14-16]. Our results revealed that the highest tertiles of RBC were associated with MetS in females, consistent with a recent study [24]. The pathogenesis of insulin resistance may, in part, be causative of the association between RBC levels and MetS. Aoki et al reported that insulin can stimulate the proliferation and differentiation of erythropoietic cells by blinding receptors upon on the cell surface [25]. It was suggested that insulin and insulin growth factors I-II can promote the proliferation and differentiation of erythroid progenitors in human bone marrow and circulation [26-28]. Alternatively, the relationship between RBC levels and MetS may be a result of iron overload. It was reported that iron overload was associated with insulin resistance [29]. Additionally, it was observed that high body iron storage interfered with insulin-mediated effects and bloodletting improved insulin sensitivity [30].

It has been reported that high HCT levels correlated with increasing risk of MetS [15-16]. Lohsoonthorn et al reported that MetS risk increased across successive quartiles of HCT in women, but not in men [31]; Nebeck et al demonstrated that HCT was significantly associated with MetS in women, but no similar trend was observed in men [16]. Our results confirmed that the ORs of MetS risk increased with the elevation of HCT in females. HCT was a major determinant of blood viscosity [32]. Increased blood viscosity causes the blood flow to skeletal muscles and fat tissues to decrease, additionally contributing to insulin resistance [33-34]. Moreover, increased blood viscosity was determined as an independent risk factor of hypertension [35]. It has been reported that HCT positively associated with insulin resistance, which is an important factor in the pathogenesis of MetS [12, 14]. Considering the bodies of evidence, we hypothesized that the association between HCT levels and MetS may arise from the increased blood viscosity and insulin resistance linked to HCT.

Hb, another important erythrocyte parameter, has been reported to be associated with MetS in both cross-sectional and cohort studies [14, 16-17, 31]. An 8-year follow-up cohort study conducted in Japan detected that the highest and third quartiles of Hb concentration were associated with increased risk of MetS incidence compared to the lowest quartiles of Hb concentration in men, but there was no

association observed in women [17]. In general, our findings were consistent with those of previous reports. In our study, the ORs for MetS increased across the successive tertiles of Hb among males; however, no similar trend was observed among females. The following mechanisms may be regarded as the causes of association between Hb and MetS: Hb is a well-known carrier and buffer of nitric oxide (NO), and can regulate the endothelial function of blood vessels by modulating NO levels in the blood [36]. Furthermore, Hb and various compounds of NO modulate the affinity between Hb and oxygen in blood, which can lead to vascular endothelial dysfunction [37]. It has been found that vascular endothelial dysfunction was associated with MetS [38-39]. In addition, Hb plays a key role in regulating sCD40L levels [40]. And sCD40L has been shown to participate in the thrombus formation and proinflammatory, which was the independent risk factor for atherosclerosis and MetS [41]. Another possibility linking Hb and MetS may be the adiponectin. Previous studies showed that higher Hb levels was closely related to lower adiponectin levels [42-43], and lower levels of adiponectin significantly increased the risk for MetS, respectively. Finally, insulin resistance may also be involved in the association between Hb and MetS [8, 12].

RDW, an common index of routine blood examination, represents a measurement of the heterogeneity in the size of circulating erythrocytes. A high RDW index indicates a greater heterogeneity in size of circulating erythrocytes in a subject. In this study, males in the highest tertiles of RDW (>13.2%) had a 2.750-fold increase in risk of MetS. Multiple groups previously showed that elevated RDW was associated with MetS [44-45]. For instance, Laufer and colleagues demonstrated that RDW ≥14% was independently associated with an increased risk for MetS development [44]; Sanchez-Chaparro and colleagues reported that the highest quartile of RDW (>14%) was remarkably linked with MetS after adjusting for potential confounders [45]. Moreover, a recent study illustrated RDW as a potential metabolic marker for the detection of metabolic diseases [46]. To date, the mechanism of association between RDW and MetS remains unknown; however, chronic inflammation linked to RDW may play an important role. It was found that MetS was associated with chronic inflammation [9], and RDW reflects an underlying inflammatory state [13]. Pierce and colleagues have proved that proinflammatory cytokines can inhibit erythropoietin-induced erythrocyte maturation, which may lead to an elevation of RDW [47].

**Conclusions**

MetS was more prevalent in females than in males. The association between erythrocyte parameters and MetS differed between sexes, whereby RBC and HCT were identified as the risk factors of MetS in females and Hb and RDW as the risk factors in males. Our study provides sufficient evidence that erythrocyte parameters may serve as effective molecular markers for the early detection of MetS risk on a sex-dependent basis.

**Acknowledgments:** We gratefully acknowledged the staff of local Community Health Service Agencies, for their kind assistance in data collection

**Contributors:** LLH and PXW conducted the data analyses. LLH, NL, XXW, LYF, XW and MJJ drafted the manuscript. PXW and DMD finalized the manuscript with inputs from all authors. All authors contributed to the development of the study framework, interpretation of the results, revisions of successive drafts of the manuscript, and approved the version submitted for publication.

**Funding** This study was supported by the Guangzhou 121 Talents Program (GZRSH-2014-2048), and by the Science and Technology Program of Guangzhou (201607010136).

**Conflicts of Interest** The authors declare that they have no conflict of interest.

**Ethical approval** The study was approved by the Ethics Committee of Guangdong Sociological Society..

**Informed consent** Informed consent was obtained from all individual participants included in the

study.

**Data sharing statement** This database is first used in this study. The database belongs to our team, and if shared, you need to get their permission.

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**Figure Legends**

**Fig 1** Proportion of metabolic syndrome (MetS) components from zero to five between males and females.

**Fig 2** Prevalence of metabolic syndrome (MetS) in association with the tertiles of red blood cell (RBC), hematocrit (HCT), hemoglobin (Hb), and red blood cell distribution width (RDW) in males and

females, separately.

**Table 1** Characteristics of study subjects with and without metabolic syndrome stratified by sex

| Variables | Male (n=2161) | | | Female (n=2511) | | |
|---|---|---|---|---|---|---|
| | MetS | Non-MetS | *P* | MetS | Non-MetS | P |
| MetS status (n, %) | 576 (26.7) | 1585 (73.3) | | 885 (35.2) | 885 (35.2) | |
| Age (years) | 51.39 ± 12.21 | 54.61 ± 13.79 | **<0.001** | 59.78 ± 12.34 | 55.70 ± 12.97 | **<0.001** |
| **Components of MetS** | | | | | | |
| WC (cm) | 89.98 ± 6.79 | 82.40 ± 7.76 | **<0.001** | 85.94 ± 7.21 | 77.59 ± 8.56 | **<0.001** |
| SBP (mmHg) | 134.93 ± 15.20 | 127.57 ± 16.32 | **<0.001** | 136.49 ± 16.42 | 124.74 ± 18.39 | **<0.001** |
| DBP (mmHg) | 89.24 ± 10.47 | 82.93 ±11.09 | **<0.001** | 84.13 ± 10.25 | 78.51 ± 10.53 | **<0.001** |
| TG (mmol/L) | 2.76 ± 1.77 | 1.29 ± 0.91 | **<0.001** | 2.15 ± 1.41 | 1.20 ± 1.87 | **<0.001** |
| HDL-C (mmol/L) | 1.00 ± 0.47 | 1.28 ± 0.44 | **<0.001** | 1.17 ± 0.22 | 1.50 ± 0.34 | **<0.001** |
| FPG (mmol/L) | 5.53 ± 2.01 | 4.87 ± 1.40 | **<0.001** | 5.38 ± 1.86 | 4.71 ± 0.97 | **<0.001** |
| **Erythrocyte parameters** | | | | | | |
| RBC ($\times 10^{12}$/L) | 4.99 ± 0.80 | 4.53 ± 0.51 | **<0.001** | 4.55 ± 0.84 | 4.10 ± 0.57 | **<0.001** |
| HCT (%) | 42.27 ± 4.09 | 40.68 ± 3.63 | **<0.001** | 37.35 ± 2.80 | 35.58 ± 2.83 | **<0.001** |
| Hb (g/L) | 147.11 ± 12.57 | 139.02 ± 12.68 | **<0.001** | 129.68 ± 14.45 | 121.50 ± 11.82 | **<0.001** |
| RDW (%) | 13.33 ± 0.96 | 12.87 ± 1.21 | **<0.001** | 13.18 ± 1.90 | 12.88 ± 2.27 | **<0.001** |
| **Liver function parameters** | | | | | | |
| ALT (u/L) | 31.44 ± 18.35 | 26.31 ± 15.52 | **<0.001** | 24.09 ± 13.81 | 21.14 ± 11.79 | **<0.001** |
| AST (u/L) | 26.37 ± 15.87 | 24.80 ± 10.00 | **0.026** | 23.82 ± 8.90 | 23.27 ± 8.63 | 0.129 |

| | | | | | | |
|---|---|---|---|---|---|---|
| GGT(u/L) | 48.73 ± 39.88 | 36.04 ± 26.83 | **<0.001** | 32.00 ± 22.79 | 26.12 ± 26.03 | **<0.001** |
| ALB (g/L) | 47.36 ± 3.23 | 47.32 ± 4.07 | 0.820 | 47.48 ± 4.32 | 47.77 ± 12.28 | 0.484 |
| **Other clinical characteristics** | | | | | | |
| BMI (kg/m$^2$) | 25.90 ± 2.67 | 23.61 ± 3.04 | **<0.001** | 25.21 ± 3.05 | 22.85 ± 3.17 | **<0.001** |
| TC (mmol/L) | 4.81 ± 0.95 | 4.73 ± 0.94 | 0.059 | 5.26 ± 1.08 | 5.08 ± 1.02 | **<0.001** |
| LDL-C (mmol/L) | 2.65 ± 0.70 | 2.66 ± 2.06 | 0.885 | 2.95 ± 1.48 | 2.75 ± 1.03 | **<0.001** |
| UA (umol/L) | 415.45 ± 143.27 | 382.19 ± 84.92 | **<0.001** | 340.60 ± 83.08 | 306.95 ± 101.63 | **<0.001** |
| WBC (×10$^9$/L) | 6.95 ± 1.40 | 6.43 ± 1.40 | **<0.001** | 6.41 ± 1.35 | 5.84 ± 1.31 | **<0.001** |
| PLT (×10$^9$/L) | 214.70 ± 49.89 | 201.57 ± 52.17 | **<0.001** | 224.04 ± 53.55 | 216.73 ± 52.14 | **0.001** |
| HbAIc (%) | 5.79 ± 1.37 | 5.42 ± 0.97 | **<0.001** | 5.64 ± 1.22 | 5.33 ± 0.67 | **<0.001** |

Data were presented as mean ± SD or *n* (%); WC, waist circumference: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; UA, uric acid; WBC, white blood cell; PLT, platelet; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; RDW, red blood cell distribution width; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALB, albumin; MetS, metabolic syndrome.

**Table 2** Levels of Erythrocyte parameters of study subjects according to number of metabolic syndrome components in males and females, respectively

| Variables | 0 | 1 | 2 | 3 | 4 | 5 | *F* | *P* |
|---|---|---|---|---|---|---|---|---|
| **Male** | | | | | | | | |
| RBC | 4.44 ± 0.53 | 4.55 ± 0.50 | 4.55 ± 0.52 | 4.80 ± 0.54 | 5.31 ± 0.86 | 5.95 ± 1.23 | 87.448 | **<0.001** |
| HCT | 39.96 ± 3.39 | 40.76 ± 3.88 | 41.00 ± 3.38 | 42.12 ± 4.10 | 42.33 ± 4.14 | 44.21 ± 3.01 | 19.799 | **<0.001** |
| Hb | 131.60 ± 12.35 | 138.81 ± 12.86 | 140.71 ± 12.41 | 144.51 ± 11.65 | 151.28 ± 12.87 | 160.04 ± 9.19 | 52.445 | **<0.001** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| RDW | 12.75 ± 0.82 | 12.83 ± 1.55 | 13.00 ± 0.80 | 13.24 ± 0.86 | 13.41 ± 1.07 | 14.33 ± 1.13 | 20.264 | **<0.001** |
| **Female** | | | | | | | | |
| RBC | 4.03 ± 0.39 | 4.07 ± 0.52 | 4.16 ± 0.54 | 4.45 ± 0.82 | 4.67 ± 0.88 | 4.83 ± 0.78 | 66.453 | **<0.001** |
| HCT | 35.16 ± 2.65 | 35.43 ± 2.78 | 35.91 ± 2.91 | 37.07 ± 2.81 | 37.74 ± 2.79 | 37.96 ± 2.36 | 52.237 | **<0.001** |
| Hb | 119.70 ± 11.54 | 121.28 ± 11.79 | 122.49 ± 11.88 | 128.26 ± 14.04 | 130.04 ± 14.35 | 139.61 ± 14.46 | 59.262 | **<0.001** |
| RDW | 12.71 ± 2.10 | 12.74 ± 1.40 | 13.07 ± 2.87 | 13.11 ± 1.39 | 13.25 ± 2.70 | 13.38 ± 1.13 | 4.493 | **<0.001** |

RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; RDW, red blood cell distribution width.

**Table 3** Odds ratios of erythrocyte parameters associated with metabolic syndrome stratified by sex

| Variables | Male | | Female | |
|---|---|---|---|---|
| | *OR (95% CI)* | *P* | *OR (95% CI)* | P |
| **RBC** | | | | |
| Q1 | | | Reference | |
| Q2 | | | — | |
| Q3 | | | 1.785 (1.248~2.554) | **0.002** |
| **HCT** | | | | |
| Q1 | | | Reference | |
| Q2 | | | 1.738 (1.229~2.458) | **0.002** |
| Q3 | | | 1.922 (1.337~2.761) | **<0.001** |
| **Hb** | | | | |
| Q1 | Reference | | | |
| Q2 | 1.687 (1.151~2.472) | **0.007** | | |
| Q3 | 2.252 (1.550~3.272) | **<0.001** | | |
| **RDW** | | | | |
| Q1 | Reference | | | |

| | | |
|---|---|---|
| Q2 | — | |
| Q3 | 2.750 (1.939~3.899) | **<0.001** |

Statistical analysis by binary logistic regression (adjusted for age, body mass index, total cholesterol, low-density lipoprotein cholesterol, uric acid, white blood cell, platelet, alanine transaminase, aspartate aminotransferase, γ-glutamyltransferase, albumin, and the components of metabolic syndrome); OR, odds ratio; CI, confidence interval; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; RDW, red blood cell distribution width.

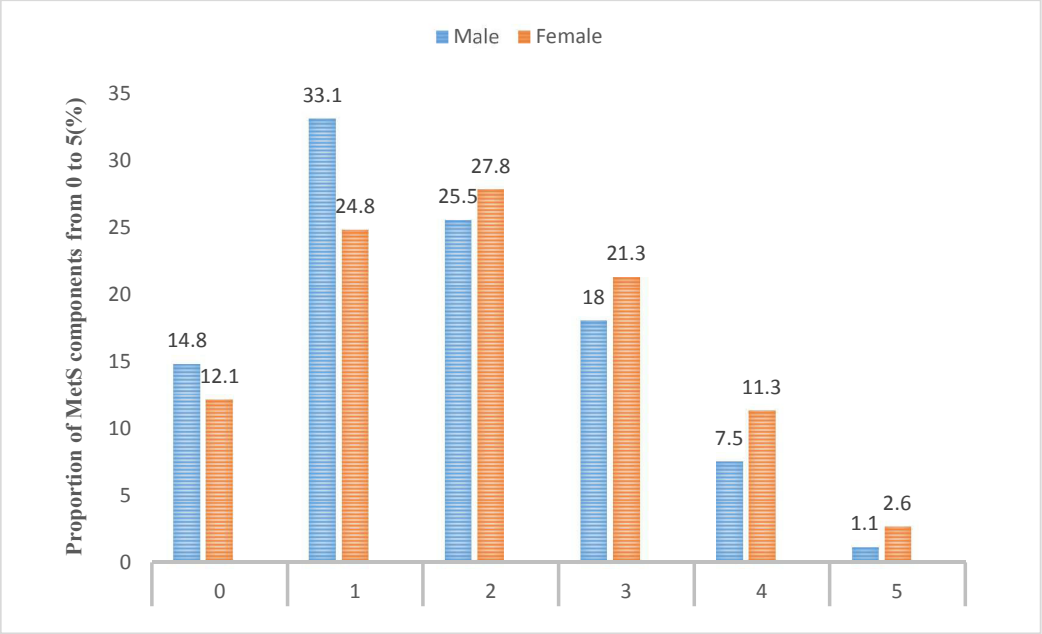


**Fig 1**

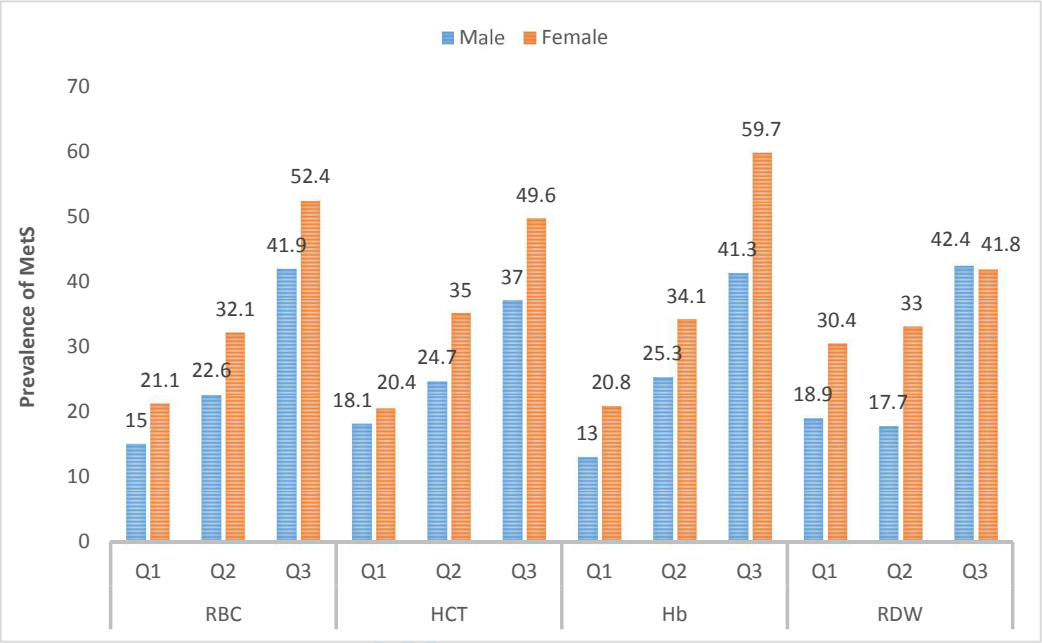


**Fig 2**

BMJ Open

# Association of erythrocyte parameters with metabolic syndrome in the Pearl River Delta region of China: a cross-sectional study



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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-019792.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 31-Oct-2017 |
| Complete List of Authors: | Huang, LingLing; Institute of Chronic Disease Risks Assessment, Henan University<br>Dou, Dong-Mei; Institute of Chronic Disease Risks Assessment, Henan University<br>Liu, Nan; Guangzhou Medical University, School of Public Health<br>Wang, XiaoXiao; Institute of Chronic Disease Risks Assessment, Henan University<br>Fu, Li-Ying; Institute of Chronic Disease Risks Assessment, Henan University<br>Wu, Xiao; Institute of Chronic Disease Risks Assessment, Henan Univercity<br>wang, peixi; Department of Preventive Medicine, School of Public Health, Guangzhou Medical University, |
| Primary Subject Heading: | Cardiovascular medicine |
| Secondary Subject Heading: | Public health, Epidemiology |
| Keywords: | Erythrocyte parameters, Metabolic syndrome, Cross-sectional study, China |
| | |

# Association of erythrocyte parameters with metabolic syndrome in the Pearl River Delta region of China: a cross-sectional study

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**Abstract**

**Objective:** Increasing studies have reported that erythrocyte parameters, including red blood cell (RBC), hematocrit (HCT), hemoglobin (Hb), and red blood cell distribution width (RDW), are associated with metabolic syndrome (MetS) in adults worldwide. However, the association, stratified by sex, remains to be elucidated, particularly in the Pearl River Delta region of China. Therefore, our /aim was to explore the association of erythrocyte parameters with MetS, stratified by sex in the Pearl River Delta region of China.

**Methods:** In this cross-sectional study, 2161 males and 2511 females were enrolled. MetS was diagnosed using a modified version of the Adult Treatment Panel III (ATP III) criteria. Logistic regression analyses were performed to calculate adjusted odds ratios (ORs) of erythrocyte parameters associated with MetS stratified by sex.

**Results:** The prevalence of MetS was higher in females than that in males (35.2% vs. 26.7%). RBC, HCT, Hb and RDW values increased linearly with the number of MetS components from zero to five identified in both males and females. Among males, the ORs of MetS risk increased across the tertiles of Hb (Q2: OR=1.687, 95% confidence interval [CI]=1.151~2.472; Q3: OR=2.252, 95%CI= 1.550~3.272). Males in the highest tertiles of RDW had a 2.750-fold increased risk of suffering from MetS compared to those in the reference group. Among females, the ORs of MetS risk increased across

the tertiles of HCT (Q2: OR=1.738, 95%CI=1.229~2.458; Q3: OR=1.922, 95%CI=1.337~2.761). Females in the highest tertiles of RBC had a 1.785-fold increased risk of experiencing MetS compared to those in the reference group.

**Conclusions:** MetS was more prevalent in females than that in males. The association between erythrocyte parameters and MetS differed between sex, whereby RBC and HCT were identified as the risk factors of MetS in females and Hb and RDW as the risk factors in males.

**Keywords:** Erythrocyte parameters, Metabolic syndrome, Cross-sectional study, China

**Strengths and limitations of this study**

- A large sample of subjects was enrolled in our survey.
- To the best of our knowledge, this is the first study to report the association of erythrocyte parameters with MetS, stratified by sex in the Pearl River Delta region of China.
- The present study was designed as a cross-sectional study; therefore, direct causation may not be concluded from the results.
- Supplementary information about the lifestyle of the subjects was not collected; therefore, these factors could not be included in the adjustments of our multivariate logistic regression analyses.

**Introduction**

Metabolic syndrome (MetS) is defined as a cluster of multiple correlated metabolic features, including abdominal obesity, hypertension, elevated triglyceride (TG) levels, decreased high-density lipoprotein cholesterol (HDL-C) levels, and hyperglycemia.[1]. It is known to be strongly associated with an increased risk of type 2 diabetes [2], cardiovascular disease (CVD) [2-4], and all-cause mortality [4]. In recent years, MetS has emerged as a global public health issue owing to its increased prevalence around the world, affecting nearly 20-30% of adults in many countries [5-7]. Hence, early identification of individuals at high risk of MetS is essential for the prevention of MetS.

Currently, the pathogenesis of MetS is not clearly understood. Generally, MetS is often accompanied by insulin resistance and/or chronic low-grade inflammation [8-9]. Numerous investigators previously reported that erythrocyte parameters levels, including red blood cell (RBC), hematocrit (HCT), hemoglobin (Hb) and red blood cell distribution width (RDW) were positively associated with a insulin resistance and chronic low grade inflammation [10-14]. In fact, RBC [14-16], HCT [15-16], Hb [14-15, 17] and RDW[18] were demonstrated in several studies worldwide to correlate with MetS in adults. However, the association between erythrocyte parameters and MetS remains controversial, because the results reported are inconsistent depending on the different ethnic populations studied. In addition, discrepancies in the results may be partly attributed to differences between sexes. Many studies simply applied sex as an adjustment variable to investigate the relationship between erythrocyte parameters and MetS, and no studies were conducted in the Pearl River Delta region of China. Therefore, the aim of this study was to explore the association between erythrocyte parameters and MetS stratified by sex in the Pearl River Delta region of China.

## Materials and Methods

### Study participants

This cross-sectional study involved participants who underwent a general health examination at the Community Health Service Agencies in the Pearl River Delta region of China in 2015. The health examination included recording of medical history, anthropometric measurements, and laboratory tests.

Participants with a history of cardiovascular diseases, severe liver and kidney dysfunction, tumors, and severe inflammatory diseases were excluded. In addition, participants who did not have complete data on their MetS components and erythrocyte parameters were excluded. Altogether, a total of 4672 subjects (2161 males and 2511 females) were enrolled in this study. The study was approved by the Ethics Committee of Guangdong Sociological Society. Written informed consent was obtained from all participants.

**Data collection and measurements**

The medical history of subjects was obtained by review of self-reported questionnaires. Anthropometric parameters were measured by trained staff, following a standardized protocol. Height, weight, waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured in replicate, and all the mean values of the above indexes were calculated for this study. Then, body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. After an overnight fast, venous blood samples from participants were obtained by measuring the blood levels of routine laboratory tests, including TG, total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), uric acid (UA), white blood cell (WBC), platelet (PLT), RBC, HCT, Hb, RDW, alanine transaminase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase;(GGT), albumin (ALB) and glycated hemoglobin A1c (HbAIc).

**Tertiles of erythrocyte parameters levels**

Erythrocyte parameters levels were categorized into tertiles on the basis of individual distributions for males and females, respectively (in males: RBC, Q1<4.37 × $10^{12}$/L, Q2=4.37~4,75 × $10^{12}$/L, Q3≥ 4.76 × $10^{12}$/L; HCT, Q1<39.8%, Q2=39.8~42.4%, Q3≥42.5%; Hb, Q1<137 g/L, Q2=137~146 g/L, Q3 ≥147 g/L; RDW, Q1<12.5%, Q2=12.5~13.1%, Q3≥13.2%; in females: RBC, Q1<3.96 × $10^{12}$/L, Q2=3.96~4,27 × $10^{12}$/L, Q3≥4.28 × $10^{12}$/L; HCT, Q1<35.2%, Q2=35.2~37.3%, Q3≥37.4%; Hb, Q1<120 g/L, Q2=120~127 g/L, Q3≥128 g/L; RDW, Q1<12.3%, Q2=12.3~12.8%, Q3≥12.9%).

**Definition of metabolic syndrome**

MetS was diagnosed using a modified version of the Adult Treatment Panel III (ATP III) criteria [1], which included at least three of the following five components: 1) WC≥90 cm in males and WC≥80 cm

in females; 2) SBP≥130 mmHg or DBP≥85 mmHg; 3) TG≥1.70 mmol/L; 4) HDL-C<1.03 mmol/L in males and HDL-C<1.29 mmol/L in females; and 5) FPG≥5.6 mmol/L.

**Statistical analysis**

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago,IL, USA). Data is presented as the mean ± standard deviation or frequency (percentage). The *t*-test was used to evaluate differences in characteristics of study subjects with and without MetS stratified by sex. The $X^2$ test was performed to compare the proportion of MetS components, from zero to five, between males and females; and compare the prevalence of MetS dependent on the tertiles of RBC, HCT, Hb, and RDW between males and females, respectively. A one-way ANOVA was conducted to test mean levels of erythrocyte parameters according to the number of MetS components in males and females, separately. Multivariate logistic regression analyses (the forward selection procedure) were performed to calculate adjusted odds ratios (ORs) of erythrocyte parameters associated with MetS stratified by sex with adjustments for potential confounders (the statistically significant variables in table 1, Male: adjusted for age, WC, SBP, DBP, TG, HDL-C, FPG, ALT, AST, GGT, BMI, UA, WBC, PLT and HbAIc; Female: adjusted for age, WC, SBP, DBP, TG, HDL-C, FPG, ALT, GGT, BMI, TC, LDL-C, UA, WBC, PLT and HbAIc). A *P* value <0.05 was considered to be statistically significant.

**Results**

**Prevalence of MetS**

In total, there were 2161 males and 2511 females enrolled in this study. Of the subjects, 576 males (26.7%) and 885 females (35.2%) were diagnosed with MetS.

**Characteristics of study subjects**

In this study, among males, the mean age of the MetS group was significantly lower than that of the non-MetS group, whereas the opposite trend was observed among females ($P$<0.001). In the cluster of MetS components, WC, SBP, DBP, TG, and FPG levels were remarkably greater in the MetS group than in the non-MetS group in both males and females, but HDL-C levels were significantly lower in the MetS group than that those the non-MetS group in both males and females ($P$<0.001). In the cluster of erythrocyte parameters, we found that RBC, HCT, Hb and RDW were significantly higher in the MetS group than those in the non-MetS group in both males and females ($P$<0.001). Additional information about the characteristics of study subjects with and without MetS stratified by sex are presented in Table 1.

**Proportion of MetS components**

Our results revealed that most males experienced one metabolic disorder, and most females suffered from two metabolic disorders. In addition, the proportion of MetS components from two to five was significantly lower in males than that in females (25.5% vs. 27.8%, 18% vs. 21.3%, 7.5% vs. 11.3%, 1.1% vs. 2.6, respectively). Additional information is shown in Fig 1.

**Association of erythrocyte parameters with MetS**

This study showed that the levels of RBC, HCT, Hb and RDW clearly increased with number of MetS components from zero to five identified in both males and females ($P$<0.001, shown in Table 2), Figure 2 showed that the prevalence of MetS increased in a dose-dependent manner as the tertiles of RBC, HCT, Hb and RDW levels increased in both males and females. Furthermore, at each tertile of the above-mentioned parameters, the prevalence of MetS was lower in males than that in females, except at the highest tertiles of RDW levels (shown in Fig 2).

**Multivariate Logistic regression analysis model**

Adjusted ORs of MetS risk associated with each tertile of RBC, HCT, Hb, and RDW are listed in Table 3. After adjusting for potential confounders (the statistically significant variables in table 1, Male: adjusted for age, WC, SBP, DBP, TG, HDL-C, FPG, ALT, AST, GGT, BMI, UA, WBC, PLT and HbAIc; Female: adjusted for age, WC, SBP, DBP, TG, HDL-C, FPG, ALT, GGT, BMI, TC, LDL-C, UA, WBC, PLT and HbAIc). a significant association of Hb and RDW with MetS was observed in males, but this was not the same for RBC and HCT. The ORs of MetS risk increased across the tertiles of Hb in males (Q2: OR=1.687, 95% confidence interval [CI]=1.151~2.472; Q3: OR=2.252, 95%CI= 1.550~3.272). Males in the highest tertiles of RDW had a 2.75-fold increased risk of suffering from

MetS in comparison to those in the reference group. Only RBC and HCT levels were observed to associate with MetS in females. The ORs of MetS risk increased across the tertiles of HCT(Q2: OR=1.738, 95% CI=1.229~2.458; Q3: OR=1.922, 95%CI=1.337~2.761). Females in the highest tertiles of RBC had a 1.785-fold increased risk of experiencing MetS in comparison to those in the reference group.

## Discussion

### Main findings

The prevalence of MetS was higher in females than that in males (35.2% vs. 26.7%). Levels of RBC, HCT, and Hb and RDW increased linearly with the number of MetS components from zero to five identified in both males and females. The association between erythrocyte parameters and MetS differed between sexes, whereby Hb and RDW were identified as risk factors of MetS in males and RBC and HCT as the risk factors in females.

### Comparisons with Previous Studies

Sex has been demonstrated to be a predictive factor for MetS development. Several studies have showed that females have a higher prevalence of MetS than that of males [19-20]. A large-scale study conducted in Russia reported that the prevalence of MetS diagnosed using the ATP III criteria, was 9.5% in men and 23.5% in women [19]; Another study performed in the seven geographical regions of Turkey showed that the prevalence of MetS as determined by the ATP III criteria, was 28% in men and 39.6% in women [20]. Our study are in accordance with the former reports. However, other studies have reported that males have a higher prevalence of MetS than that of females. For example, Tao et al found the 5-year cumulative incidence of MetS in Beijing adults was 14.22% for males and 7.59% for females [21]; Yang et al revealed that the 5-year cumulative incidence of MetS in Taiwanese adults was 14.95% for males and 9.89% for females [22]. The difference in the findings might be due to the different study design and population.

It is well known that MetS represents a cluster of simultaneously occurring metabolic abnormalities. In fact, previous studies demonstrated that RBC and Hb levels clearly increased with the

numbers of MetS components [16. 23]. Our findings were consistent with those of these reports. It has also been shown that a higher number of MetS components is associated with insulin resistance. Based on the facts that the levels of RBC, HCT and Hb were significantly associated with insulin resistance [10, 12, 24], we hypothesize that increased levels of erythrocyte parameters tested in this study may be indicative of the development of insulin resistance.

Many studies have demonstrated an association between RBC levels and MetS, indicating RBC is a potential hematological marker for early detection of MetS [14-16]. Our results revealed that the highest tertiles of RBC were associated with MetS in females, consistent with a recent study [24]. The pathogenesis of insulin resistance may, in part, be causative of the association between RBC levels and MetS. Aoki et al reported that insulin can stimulate the proliferation and differentiation of erythropoietic cells by blinding receptors upon the cell surface [26]. It was suggested that insulin and insulin growth factors I-II can promote the proliferation and differentiation of erythroid progenitors in human bone marrow and circulation [27-29]. Alternatively, the relationship between RBC levels and MetS may be a result of iron overload. It was reported that iron overload was associated with insulin resistance [30], and high body iron storage interfered with insulin-mediated effects and bloodletting improved insulin sensitivity [31]. Bozzini et al found that iron overload was strongly associated with obesity and dyslipidemia, and serum ferritin would help identify a subgroup of individuals at risk for insulin resistance-associated hepatic iron overload.[32]. Additionally, the erythrocyte fatty acids composition changes may play a major role in the association of RBC levels with MetS. Novgorodtseva et al found that the development of MetS was accompanied by erythrocyte fatty acids composition changes [33], and Zong et al demonstrated that erythrocyte fatty acids in the de novo lipogenesis pathway were independently associated with an elevated risk of MetS [34]. It has been reported that insulin resistance could link fatty acids with MetS [35].

It has been reported that high HCT levels correlated with increasing risk of MetS [15-16]. Lohsoonthorn et al reported that MetS risk increased across successive quartiles of HCT in females, but not in males [36]; Nebeck et al demonstrated that HCT was significantly associated with MetS in females, but no similar trend was observed in males [16]. Our results confirmed that the ORs of MetS risk increased with an elevation in HCT in females. HCT was considered as a major determinant of blood viscosity [37]. Increased blood viscosity causes blood flow to skeletal muscles and fat tissues to

decrease, additionally contributing to insulin resistance [38-39]. Moreover, increased blood viscosity was determined as an independent risk factor of hypertension [40]. It has been reported that HCT is positively associated with insulin resistance, which is an important factor in the pathogenesis of MetS [12, 14]. Considering these bodies of evidence, we hypothesize that the association between HCT levels and MetS may arise from increased blood viscosity and insulin resistance linked to HCT.

Hb, another important erythrocyte parameter, has been reported to be associated with MetS in both cross-sectional and cohort studies [14, 16-17, 36]. An 8-year follow-up cohort study conducted in Japan detected that the highest and third quartiles of Hb concentration were associated with increased risk of MetS incidence compared to the lowest quartiles of Hb concentration in males, but there was no association observed in females [17]. In general, our findings were consistent with those of the previous reports. In our study, the ORs of MetS increased across the successive tertiles of Hb among males; however, no similar trend was observed among females. The following mechanisms may be regarded as the causes of association between Hb and MetS: Hb is a well-known carrier and buffer of nitric oxide (NO), and can regulate the endothelial function of blood vessels by modulating NO levels in blood [41]. Furthermore, Hb and various compounds of NO modulate the affinity between Hb and oxygen in blood, which can lead to vascular endothelial dysfunction [42]. It has been found that vascular endothelial dysfunction was associated with MetS [43-44]. In addition, Hb plays a key role in regulating sCD40L levels [45], and sCD40L has been shown to participate in thrombus formation and inflammation, which is a independent risk factor for atherosclerosis and MetS [46]. Another possibility linking Hb and MetS may be the adiponectin. Previous studies showed that higher Hb levels were closely related to the lower adiponectin levels [47-48], and lower levels of adiponectin significantly increased the risk for MetS, respectively. Finally, insulin resistance may also be involved in the association between Hb and MetS [8, 12].

RDW, a common index of routine blood examination, represents a measure of heterogeneity in the size of circulating erythrocytes. A high RDW index indicates greater heterogeneity in size of circulating erythrocytes in a subject. In this study, males in the highest tertiles of RDW (>13.2%) had a 2.75-fold increased risk for MetS. Multiple groups previously showed that elevated RDW was associated with MetS [49-50]. For instance, Laufer and colleagues demonstrated that RDW ≥14% was independently associated with an increased risk for MetS development [49]; Sanchez-Chaparro and colleagues

reported that the highest quartile of RDW (>14%) was remarkably linked with MetS after adjusting for potential confounders [50]. Moreover, a recent study illustrated RDW is a potential metabolic marker for the detection of metabolic diseases [51]. To date, the mechanism of association between RDW and MetS remains unknown; however, chronic inflammation linked to RDW may play an important role. It was found that MetS was associated with chronic inflammation [9], and RDW reflects an underlying inflammatory state [13]. Pierce and colleagues have proved that proinflammatory cytokines can inhibit erythropoietin-induced erythrocyte maturation, which may lead to an elevation of RDW [52].

However, there were several limitations in this study. First, the present study was designed as a cross-sectional study; therefore, direct causation cannot be concluded from the results. Then, supplementary information about the lifestyle of the subjects was not collected; therefore, these factors could not be included in the adjustments of our multivariate logistic regression analyses. It was found that people from the Pearl River Delta region of China often seldom eat breakfast, stay up late and lack physical exercise [53]. In addition, Han and his colleague reported that the smoking rate of people over 15 years old in Shenzhen was higher than that in the whole country (22.32% vs. 22.30%) [54-55]. It is well known that these factors are related to the development of MetS.



## Conclusions

In our study, MetS was more prevalent in females than that in males. The association between erythrocyte parameters and MetS differed between sexes, whereby RBC and HCT were identified as the risk factors of MetS in females and Hb and RDW as the risk factors in males. Our study provides sufficient evidence that erythrocyte parameters may serve as effective molecular markers for the early detection of MetS risk on a sex-dependent basis.

**Acknowledgments:** We gratefully acknowledge the staff of local Community Health Service Agencies, for their kind assistance in data collection

**Contributors:** LLH and PXW conducted the data analyses. LLH, NL, XXW, LYF and XW drafted the manuscript. PXW and DMD finalized the manuscript with inputs from all authors. All authors contributed to the development of the study framework, interpretation of the results, revisions of successive drafts of the manuscript, and approved the version submitted for publication.

**Funding** This study was supported by the Guangzhou 121 Talents Program (GZRSH-2014-2048), the Science and Technology Program of Guangzhou (201607010136, 201510010109) and the National Science Foundation of China (81402716).

**Conflicts of Interest** The authors declare that they have no conflicts of interest.

**Ethical approval** The study was approved by the Ethics Committee of Guangdong Sociological Society..

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Data sharing statement** This database is first used in this study. The database belongs to our team, and if shared, you need to get their permission.

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**Figure Legends**

**Figure 1** Proportion of metabolic syndrome (MetS) components from zero to five between males and females.

**Figure 2** Prevalence of metabolic syndrome (MetS) in association with the tertiles of red blood cell (RBC), hematocrit (HCT), hemoglobin (Hb), and red blood cell distribution width (RDW) in males and females, separately.

**Table 1** Characteristics of study subjects with and without metabolic syndrome stratified by sex

| | Male (n=2161) | | | Female (n=2511) | | |
|---|---|---|---|---|---|---|
| Variables | MetS | Non-MetS | *P* | MetS | Non-MetS | *P* |
| MetS status (n, %) | 576 (26.7) | 1585 (73.3) | | 885 (35.2) | 885 (35.2) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Age (years) | 51.39 ± 12.21 | 54.61 ± 13.79 | **<0.001** | 59.78 ± 12.34 | 55.70 ± 12.97 | **<0.001** |
| **Components of MetS** | | | | | | |
| WC (cm) | 89.98 ± 6.79 | 82.40 ± 7.76 | **<0.001** | 85.94 ± 7.21 | 77.59 ± 8.56 | **<0.001** |
| SBP (mmHg) | 134.93 ± 15.20 | 127.57 ± 16.32 | **<0.001** | 136.49 ± 16.42 | 124.74 ± 18.39 | **<0.001** |
| DBP (mmHg) | 89.24 ± 10.47 | 82.93 ±11.09 | **<0.001** | 84.13 ± 10.25 | 78.51 ± 10.53 | **<0.001** |
| TG (mmol/L) | 2.76 ± 1.77 | 1.29 ± 0.91 | **<0.001** | 2.15 ± 1.41 | 1.20 ± 1.87 | **<0.001** |
| HDL-C (mmol/L) | 1.00 ± 0.47 | 1.28 ± 0.44 | **<0.001** | 1.17 ± 0.22 | 1.50 ± 0.34 | **<0.001** |
| FPG (mmol/L) | 5.53 ± 2.01 | 4.87 ± 1.40 | **<0.001** | 5.38 ± 1.86 | 4.71 ± 0.97 | **<0.001** |
| **Erythrocyte parameters** | | | | | | |
| RBC ($\times 10^{12}$/L) | 4.99 ± 0.80 | 4.53 ± 0.51 | **<0.001** | 4.55 ± 0.84 | 4.10 ± 0.57 | **<0.001** |
| HCT (%) | 42.27 ± 4.09 | 40.68 ± 3.63 | **<0.001** | 37.35 ± 2.80 | 35.58 ± 2.83 | **<0.001** |
| Hb (g/L) | 147.11 ± 12.57 | 139.02 ± 12.68 | **<0.001** | 129.68 ± 14.45 | 121.50 ± 11.82 | **<0.001** |
| RDW (%) | 13.33 ± 0.96 | 12.87 ± 1.21 | **<0.001** | 13.18 ± 1.90 | 12.88 ± 2.27 | **<0.001** |
| **Liver function parameters** | | | | | | |
| ALT (u/L) | 31.44 ± 18.35 | 26.31 ± 15.52 | **<0.001** | 24.09 ± 13.81 | 21.14 ± 11.79 | **<0.001** |
| AST (u/L) | 26.37 ± 15.87 | 24.80 ± 10.00 | **0.026** | 23.82 ± 8.90 | 23.27 ± 8.63 | 0.129 |
| GGT(u/L) | 48.73 ± 39.88 | 36.04 ± 26.83 | **<0.001** | 32.00 ± 22.79 | 26.12 ± 26.03 | **<0.001** |
| ALB (g/L) | 47.36 ± 3.23 | 47.32 ± 4.07 | 0.820 | 47.48 ± 4.32 | 47.77 ± 12.28 | 0.484 |
| **Other clinical characteristics** | | | | | | |
| BMI (kg/m$^2$) | 25.90 ± 2.67 | 23.61 ± 3.04 | **<0.001** | 25.21 ± 3.05 | 22.85 ± 3.17 | **<0.001** |

| | | | | | | |
|---|---|---|---|---|---|---|
| TC (mmol/L) | 4.81 ± 0.95 | 4.73 ± 0.94 | 0.059 | 5.26 ± 1.08 | 5.08 ± 1.02 | **<0.001** |
| LDL-C (mmol/L) | 2.65 ± 0.70 | 2.66 ± 2.06 | 0.885 | 2.95 ± 1.48 | 2.75 ± 1.03 | **<0.001** |
| UA (umol/L) | 415.45 ± 143.27 | 382.19 ± 84.92 | **<0.001** | 340.60 ± 83.08 | 306.95 ± 101.63 | **<0.001** |
| WBC ($\times 10^9$/L) | 6.95 ± 1.40 | 6.43 ± 1.40 | **<0.001** | 6.41 ± 1.35 | 5.84 ± 1.31 | **<0.001** |
| PLT ($\times 10^9$/L) | 214.70 ± 49.89 | 201.57 ± 52.17 | **<0.001** | 224.04 ± 53.55 | 216.73 ± 52.14 | **0.001** |
| HbAIc (%) | 5.79 ± 1.37 | 5.42 ± 0.97 | **<0.001** | 5.64 ± 1.22 | 5.33 ± 0.67 | **<0.001** |

Data were presented as mean ± SD or *n* (%); MetS, metabolic syndrome; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; RBC, red blood cell; HCT, hematocrit; Hb, hemoglobin; RDW, red blood cell distribution width; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ALB, albumin; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; WBC, white blood cell; PLT, platelet; HbAIc, glycated hemoglobin A1c.

**Table 2** Levels of erythrocyte parameters of study subjects according to number of metabolic syndrome components in males and females, respectively

| Variables | 0 | 1 | 2 | 3 | 4 | 5 | *F* | *P* |
|---|---|---|---|---|---|---|---|---|
| **Male** | | | | | | | | |
| RBC | 4.44 ± 0.53 | 4.55 ± 0.50 | 4.55 ± 0.52 | 4.80 ± 0.54 | 5.31 ± 0.86 | 5.95 ± 1.23 | 87.448 | **<0.001** |
| HCT | 39.96 ± 3.39 | 40.76 ± 3.88 | 41.00 ± 3.38 | 42.12 ± 4.10 | 42.33 ± 4.14 | 44.21 ± 3.01 | 19.799 | **<0.001** |
| Hb | 131.60 ± 12.35 | 138.81 ± 12.86 | 140.71 ± 12.41 | 144.51 ± 11.65 | 151.28 ± 12.87 | 160.04 ± 9.19 | 52.445 | **<0.001** |
| RDW | 12.75 ± 0.82 | 12.83 ± 1.55 | 13.00 ± 0.80 | 13.24 ± 0.86 | 13.41 ± 1.07 | 14.33 ± 1.13 | 20.264 | **<0.001** |
| **Female** | | | | | | | | |
| RBC | 4.03 ± 0.39 | 4.07 ± 0.52 | 4.16 ± 0.54 | 4.45 ± 0.82 | 4.67 ± 0.88 | 4.83 ± 0.78 | 66.453 | **<0.001** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| HCT | 35.16 ± 2.65 | 35.43 ± 2.78 | 35.91 ± 2.91 | 37.07 ± 2.81 | 37.74 ± 2.79 | 37.96 ± 2.36 | 52.237 | **<0.001** |
| Hb | 119.70 ± 11.54 | 121.28 ± 11.79 | 122.49 ± 11.88 | 128.26 ± 14.04 | 130.04 ± 14.35 | 139.61 ± 14.46 | 59.262 | **<0.001** |
| RDW | 12.71 ± 2.10 | 12.74 ± 1.40 | 13.07 ± 2.87 | 13.11 ± 1.39 | 13.25 ± 2.70 | 13.38 ± 1.13 | 4.493 | **<0.001** |

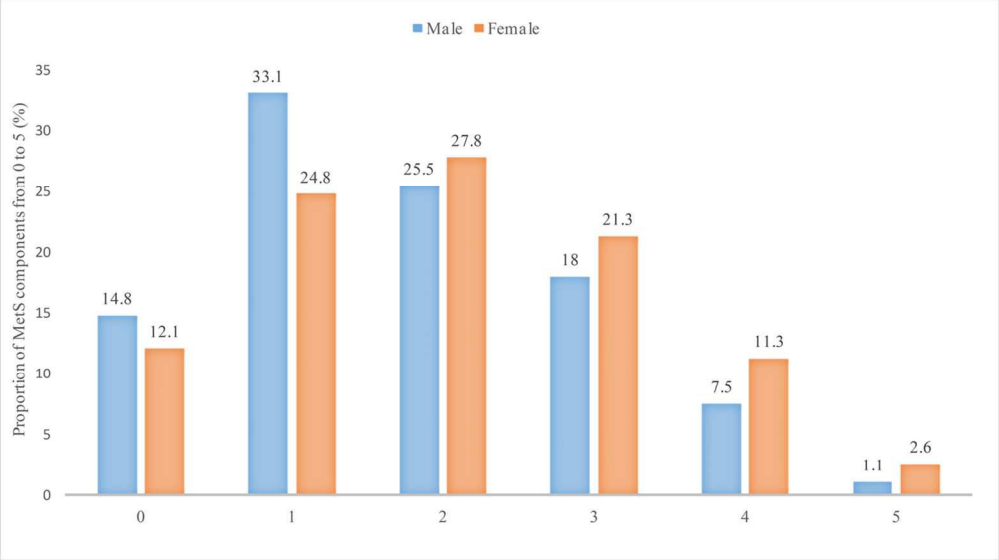
RBC, red blood cell; HCT, hematocrit; Hb, hemoglobin; RDW, red blood cell distribution width.

**Table 3** Odds ratios of erythrocyte parameters associated with metabolic syndrome stratified by sex

| Variables | Male | | Female | |
|---|---|---|---|---|
| | *OR (95% CI)* | *P* | *OR (95% CI)* | P |
| **Age** | — | 0.918 | — | 0.161 |
| **WC** | 1.149 (1.123~1.176) | **<0.001** | 1.139 (1.119~1.160) | **<0.001** |
| **SBP** | 1.027 (1.015~1.039) | **<0.001** | 1.044 (1.035~1.054) | **<0.001** |
| **DBP** | 1.024 (1.006~1.042) | **0.007** | 1.024 (1.009~1.040) | **0.002** |
| **TG** | 3.401 (2.844~4.068) | **<0.001** | 1.538 (1.287~1.838) | **<0.001** |
| **HDL-C** | 0.026 (0.013~0.054) | **<0.001** | 0.001 (0.001~0.003) | **<0.001** |
| **FPG** | 1.551 (1.415~1.700) | **<0.001** | 2.214 (1.832~2.676) | **<0.001** |
| **ALT** | — | 0.249 | — | 0.702 |
| **AST** | — | 0.163 | | |
| **GGT** | — | 0.230 | 1.006 (1.001~1.010) | **0.014** |
| **BMI** | — | 0.627 | — | 0.747 |
| **TC** | | | 1.274 (1.115~1.457) | **<0.001** |
| **LDL-C** | | | — | 0.776 |
| **UA** | — | 0.272 | — | 0.156 |
| **WBC** | — | 0.205 | — | 0.202 |
| **PLT** | — | 0.088 | — | 0.636 |

| | | | | |
|---|---|---|---|---|
| **HbAIc** | — | 0.189 | 0.761 (0.584~0.992) | **0.044** |
| **RBC** | | | | |
| Q1 | Reference | | Reference | |
| Q2 | — | 0.148 | 1.129 (0.792~1.610) | 0.502 |
| Q3 | — | 0.099 | 1.785 (1.248~2.554) | **0.002** |
| **HCT** | | | | |
| Q1 | Reference | | Reference | |
| Q2 | — | 0.134 | 1.738 (1.229~2.458) | **0.002** |
| Q3 | — | 0.268 | 1.922 (1.337~2.761) | **<0.001** |
| **Hb** | | | | |
| Q1 | Reference | | Reference | |
| Q2 | 1.687 (1.151~2.472) | **0.007** | — | 0.515 |
| Q3 | 2.252 (1.550~3.272) | **<0.001** | — | 0.173 |
| **RDW** | | | | |
| Q1 | Reference | | Reference | |
| Q2 | 1.110 (0.758~1.625) | 0.593 | — | 0.068 |
| Q3 | 2.750 (1.939~3.899) | **<0.001** | — | 0.398 |

OR, odds ratio; CI, confidence interval; Statistical analysis by binary logistic regression with adjustments for potential confounders (the statistically significant variables in table 1, Male: adjusted for age, WC [waist circumference], SBP [systolic blood pressure], DBP [diastolic blood pressure], TG [triglyceride], HDL-C [high-density lipoprotein cholesterol], FPG [fasting plasma glucose], ALT [alanine transaminase], AST [aspartate aminotransferase], GGT [γ-glutamyltransferase], BMI [body mass index], UA [uric acid], WBC [white blood cell], PLT [platelet] and HbAIc [glycated hemoglobin A1c]; Female: adjusted for age, WC, SBP, DBP, TG, HDL-C, FPG, ALT, GGT, BMI, TC [total cholesterol], LDL-C [low-density lipoprotein cholesterol],, UA, WBC, PLT and HbAIc); RBC, red blood cell; HCT, hematocrit; Hb, hemoglobin; RDW, red blood cell distribution width.

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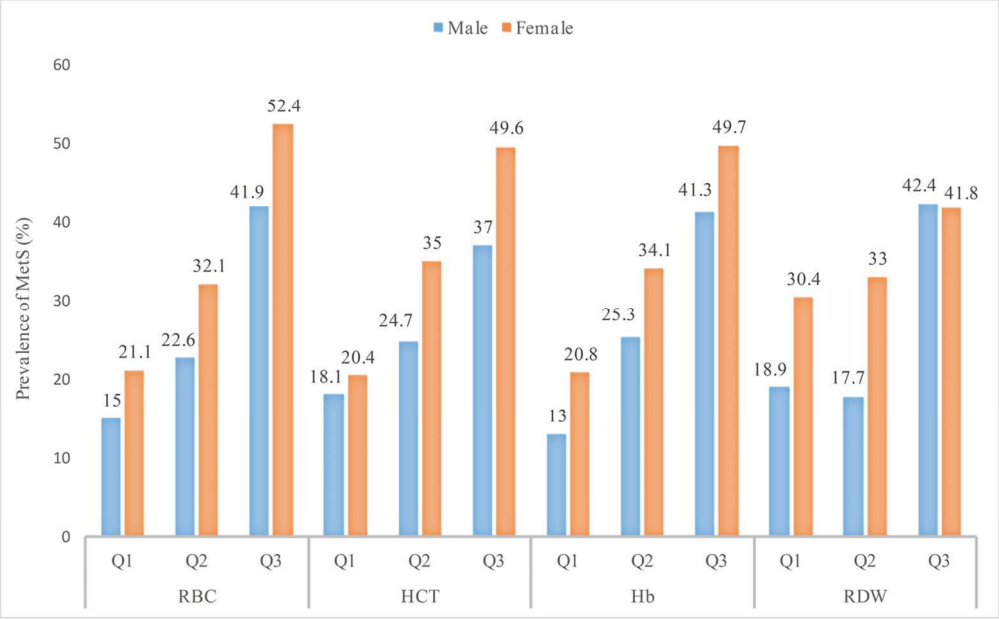


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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract (Page 1) |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Page 2) |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported (Page 4) |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses (Page 4) |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper (Page 4) |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page 4) |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants (Page 4-5) |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Page 5-6) |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Page 5) |
| Bias | 9 | Describe any efforts to address potential sources of bias (Page 5) |
| Study size | 10 | Explain how the study size was arrived at (Page 4-5) |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (5-6) |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding (Page 6) |
| | | (*b*) Describe any methods used to examine subgroups and interactions (Page 6) |
| | | (*c*) Explain how missing data were addressed (Page 4-5) |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy (not applicable) |
| | | (*e*) Describe any sensitivity analyses (Page 6) |
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Table 1) |
| | | (b) Give reasons for non-participation at each stage (not applicable) |
| | | (c) Consider use of a flow diagram (Not applicable) |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Page 6-7, Table 1-2, Figure 1-2) |
| | | (b) Indicate number of participants with missing data for each variable of interest (Not applicable) |
| Outcome data | 15* | Report numbers of outcome events or summary measures (Page 6, Table 1) |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were |

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| | | adjusted for and why they were included (Page 7, Table 3) |
| | | (*b*) Report category boundaries when continuous variables were categorized (Page 5) |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (Not applicable) |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Not applicable) |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives (Page 7) |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (Page 10-11) |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Page 8-10) |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results (Page 11) |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (Page 11) |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# Association of erythrocyte parameters with metabolic syndrome in the Pearl River Delta region of China: a cross-sectional study



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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-019792.R2 |
| Article Type: | Research |
| Date Submitted by the Author: | 14-Nov-2017 |
| Complete List of Authors: | Huang, LingLing; Institute of Chronic Disease Risks Assessment, Henan University<br>Dou, Dong-Mei; Institute of Chronic Disease Risks Assessment, Henan University<br>Liu, Nan; Guangzhou Medical University, School of Public Health<br>Wang, XiaoXiao; Institute of Chronic Disease Risks Assessment, Henan University<br>Fu, Li-Ying; Institute of Chronic Disease Risks Assessment, Henan University<br>Wu, Xiao; Institute of Chronic Disease Risks Assessment, Henan Univercity<br>wang, peixi; Department of Preventive Medicine, School of Public Health, Guangzhou Medical University, |
| Primary Subject Heading: | Cardiovascular medicine |
| Secondary Subject Heading: | Public health, Epidemiology |
| Keywords: | Erythrocyte parameters, Metabolic syndrome, Cross-sectional study, China |
| | |

# Association of erythrocyte parameters with metabolic syndrome in the Pearl River Delta region of China: a cross-sectional study

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**Abstract**

**Objective:** Increasing studies have reported that erythrocyte parameters, including red blood cell (RBC), hematocrit (HCT), hemoglobin (Hb), and red blood cell distribution width (RDW), are associated with metabolic syndrome (MetS) in adults worldwide. However, the association, stratified by sex, remains to be elucidated, particularly in the Pearl River Delta region of China. Therefore, our aim was to explore the association of erythrocyte parameters with MetS, stratified by sex in the Pearl River Delta region of China.

**Methods:** In this cross-sectional study, 2161 males and 2511 females were enrolled. MetS was diagnosed using a modified version of the Adult Treatment Panel III (ATP III) criteria. Logistic regression analyses were performed to calculate adjusted odds ratios (ORs) of erythrocyte parameters associated with MetS stratified by sex.

**Results:** The prevalence of MetS was higher in females than that in males (35.2% vs.26.7%). RBC, HCT, Hb and RDW values increased linearly with the number of MetS components from zero to five identified in both males and females. Among males, the ORs of MetS risk increased across the tertiles of Hb (Q2: OR=1.921, 95% confidence interval [CI]=1.170~3.151; Q3: OR=1.992, 95%CI= 1.198~3.312). Males in the highest tertiles of RDW had a 2.752-fold increased risk of suffering from MetS compared to those in the reference group. Among females, the ORs of MetS risk also increased across the tertiles of Hb (Q2: OR=1.538, 95%CI=1.008~2.348; Q3: OR=1.665, 95%CI=1.075~2.578). Females in the highest tertiles of RBC had a 1.718-fold increased risk of experiencing MetS compared to those in the reference group.

**Conclusions:** MetS was more prevalent in females than that in males. The association between erythrocyte parameters and MetS differed between sex, whereby RBC and Hb were identified as the risk factors of MetS in females and Hb and RDW as the risk factors in males.

**Keywords:** Erythrocyte parameters, Metabolic syndrome, Cross-sectional study, China

**Strengths and limitations of this study**

- A large sample of subjects was enrolled in our survey.
- To the best of our knowledge, this is the first study to report the association of erythrocyte parameters with MetS, stratified by sex in the Pearl River Delta region of China.
- The present study was designed as a cross-sectional study; therefore, direct causation may not be concluded from the results.
- Supplementary information about the lifestyle of the subjects was not collected; therefore, these factors could not be included in the adjustments of our multivariate logistic regression analyses.

## Introduction

Metabolic syndrome (MetS) is defined as a cluster of multiple correlated metabolic features, including abdominal obesity, hypertension, elevated triglyceride (TG) levels, decreased high-density lipoprotein cholesterol (HDL-C) levels, and hyperglycemia [1]. It is known to be strongly associated with an increased risk of type 2 diabetes [2], cardiovascular disease (CVD) [2-4], and all-cause mortality [4]. In recent years, MetS has emerged as a global public health issue owing to its increased prevalence around the world, affecting nearly 20-30% of adults in many countries [5-7]. Hence, early identification of individuals at high risk of MetS is essential for the prevention of MetS.

Currently, the pathogenesis of MetS is not clearly understood. Generally, MetS is often accompanied by insulin resistance and/or chronic low-grade inflammation [8-9].Numerous investigators previously reported that erythrocyte parameters, including red blood cell count (RBC), hematocrit (HCT), hemoglobin (Hb) and red blood cell distribution width (RDW) were positively associated with insulin resistance and chronic low-grade inflammation [10-14]. In fact, RBC [14-16], HCT [15-16], Hb [14-15, 17] and RDW [18] were demonstrated in several studies worldwide to correlate with MetS in adults. However, the association between erythrocyte parameters and MetS remains controversial, because the results reported are inconsistent depending on the different ethnic populations studied. In addition, discrepancies in the results may be partly attributed to differences between sexes. Many studies simply applied sex as an adjustment variable to investigate the relationship between erythrocyte parameters and MetS, and no studies were conducted in the Pearl River Delta region of China. Therefore, the aim of this study was to explore the association between erythrocyte parameters and MetS stratified by sex in the Pearl River Delta region of China.

## Materials and Methods

### Study participants

This cross-sectional study involved participants who underwent a general health examination at the Community Health Service Agencies in the Pearl River Delta region of China in 2015. The health examination included recording of medical history, anthropometric measurements, and laboratory tests. Participants with a history of cardiovascular diseases, severe liver and kidney dysfunction, tumors, and severe inflammatory diseases were excluded. In addition, participants who did not have complete data on their MetS components and erythrocyte parameters were excluded. Altogether, a total of 4672

subjects (2161 males and 2511 females) were enrolled in this study. The study was approved by the Ethics Committee of Guangdong Sociological Society. Written informed consent was obtained from all participants.

**Data collection and measurements**

The medical history of subjects was obtained by review of self-reported questionnaires. Anthropometric parameters were measured by trained staff, following a standardized protocol. Height, weight, waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured in replicate, and all the mean values of the above indexes were calculated. Then, body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. After an overnight fast, venous blood samples from participants were obtained and analysed for TG, total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol(LDL-C), fasting plasma glucose (FPG), uric acid (UA), white blood cell (WBC), platelet (PLT), RBC, HCT, Hb, RDW, alanine transaminase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase;(GGT), albumin (ALB) and glycated hemoglobin A1c (HbAIc).

**Quality control**

All data are collected by trained doctors or nurses. They are strict in checking the data of every participant. In addition, several supervisors were arranged to verify the authenticity of the data.

**Tertiles of erythrocyte parameters levels**

Erythrocyte parameters levels were categorized into tertiles on the basis of individual distributions for males and females, respectively (in males: RBC, Q1<4.37 $\times 10^{12}$/L, Q2=4.37~4,75 $\times 10^{12}$/L, Q3≥ 4.76 $\times 10^{12}$/L; HCT, Q1<39.8%, Q2=39.8~42.4%, Q3≥42.5%; Hb, Q1<137 g/L, Q2=137~146 g/L, Q3 ≥147 g/L; RDW, Q1<12.5%, Q2=12.5~13.1%, Q3≥13.2%; in females: RBC, Q1<3.96 $\times 10^{12}$/L, Q2=3.96~4,27 $\times 10^{12}$/L, Q3≥4.28 $\times 10^{12}$/L; HCT, Q1<35.2%, Q2=35.2~37.3%, Q3≥37.4%; Hb, Q1<120 g/L, Q2=120~127 g/L, Q3≥128 g/L; RDW, Q1<12.3%, Q2=12.3~12.8%, Q3≥12.9%).

**Definition of metabolic syndrome**

MetS was diagnosed using a modified version of the Adult Treatment Panel III (ATP III) criteria [1], which included at least three of the following five components: 1) WC≥90 cm in males and WC≥80 cm in females; 2) SBP≥130 mmHg or DBP≥85 mmHg; 3) TG≥1.70 mmol/L; 4) HDL-C<1.03 mmol/L in males and HDL-C<1.29 mmol/L in females; and 5) FPG≥5.6 mmol/L.

**Statistical analysis**

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago, IL, USA). Data is presented as the mean ± standard deviation or frequency(percentage). The *t*-test was used to evaluate differences in characteristics of study subjects with and without MetS stratified by sex. The $X^2$ test was performed to compare the proportion of MetS components, from zero to five, between males and females; and compare the prevalence of MetS dependent on the tertiles of RBC, HCT, Hb, and RDW between males and females, respectively. A one-way ANOVA was conducted to test mean levels of erythrocyte parameters according to the number of MetS components in males and females, separately. Multivariate logistic regression analyses (the enter selection procedure) were performed to calculate adjusted odds ratios (ORs) of erythrocyte parameters associated with MetS stratified by sex with adjustments for potential confounders (the statistically significant variables in table 1, Male: adjusted for age, WC, SBP, DBP, TG, HDL-C, FPG, ALT, AST, GGT, BMI, UA, WBC, PLT and HbAIc; Female: adjusted for age, WC, SBP, DBP, TG, HDL-C, FPG, ALT, GGT, BMI, TC, LDL-C, UA, WBC, PLT and HbAIc). A *P* value <0.05 was considered to be statistically significant.

**Results**

**Prevalence of MetS**

In total, there were 2161 males and 2511 females enrolled in this study. Of the subjects, 576 males (26.7%) and 885 females (35.2%) were diagnosed with MetS.

**Characteristics of study subjects**

In this study, among males, the mean age of the MetS group was significantly lower than that of the non-MetS group, whereas the opposite trend was observed among females ($P<0.001$). In the cluster of MetS components, WC, SBP, DBP, TG, and FPG levels were remarkably greater in the MetS group than in the non-MetS group in both males and females, but HDL-C levels were significantly lower in the MetS group than that those the non-MetS group in both males and females ($P<0.001$). In the cluster of erythrocyte parameters, we found that RBC, HCT, Hb and RDW were significantly higher in the MetS group than those in the non-MetS group in both males and females ($P<0.001$). Additional information about the characteristics of study subjects with and without MetS stratified by sex are presented in Table 1.

**Proportion of MetS components**

Our results revealed that most males experienced one metabolic disorder, and most females suffered from two metabolic disorders. In addition, the proportion of MetS components from two to five was significantly lower in males than that in females (25.5% vs. 27.8%, 18% vs. 21.3%, 7.5% vs. 11.3%, 1.1% vs. 2.6, respectively). Additional information is shown in Fig 1.

**Association of erythrocyte parameters with MetS**

This study showed that the levels of RBC, HCT, Hb and RDW clearly increased with number of MetS components from zero to five identified in both males and females ($P$<0.001, shown in Table 2), Figure 2 showed that the prevalence of MetS increased in a dose-dependent manner as the tertiles of RBC, HCT, Hb and RDW levels increased in both males and females. Furthermore, at each tertile of the above-mentioned parameters, the prevalence of MetS was lower in males than that in females, except at the highest tertiles of RDW levels (shown in Fig 2).

**Multivariate Logistic regression analysis model**

Adjusted ORs of MetS risk associated with each tertile of RBC, HCT, Hb, and RDW are listed in Table 3. After adjusting for potential confounders (the statistically significant variables in table 1, Male: adjusted for age, WC, SBP, DBP, TG, HDL-C, FPG, ALT, AST, GGT,BMI, UA, WBC, PLT and HbAIc; Female: adjusted for age, WC, SBP, DBP, TG, HDL-C,FPG, ALT, GGT,BMI, TC, LDL-C, UA, WBC, PLT and HbAIc). A significant association of Hb and RDW with MetS was observed in males, but this was not the same for RBC and HCT. The ORs of MetS risk increased across the tertiles of Hb (Q2: OR=1.921, 95% confidence interval [CI]=1.170~3.151; Q3: OR=1.992, 95%CI= 1.198~3.312). Males in the highest tertiles of RDW had a 2.752-fold increased risk of suffering from MetS compared to those in the reference group. Only RBC and Hb levels were observed to associate with MetS in females. The ORs of MetS risk also increased across the tertiles of Hb (Q2: OR=1.538, 95%CI=1.008~2.348; Q3: OR=1.665, 95%CI=1.075~2.578). Females in the highest tertiles of RBC had a 1.718-fold increased risk of experiencing MetS in comparison to those in the reference group.

**Discussion**

**Main findings**

The prevalence of MetS was higher in females than that in males (35.2% vs. 26.7%). Levels of RBC,

HCT, Hb and RDW increased linearly with the number of MetS components from zero to five identified in both males and females. The association between erythrocyte parameters and MetS differed between sexes, whereby Hb and RDW were identified as risk factors of MetS in males and RBC and Hb as the risk factors in females.

**Comparisons with Previous Studies**

Sex has been demonstrated to be a predictive factor for MetS development. Several studies have showed that females have a higher prevalence of MetS than males [19-20]. A large-scale study conducted in Russia reported that the prevalence of MetS diagnosed using the ATP III criteria, was 9.5% in men and 23.5% in women [19]; Another study performed in the seven geographical regions of Turkey showed that the prevalence of MetS as determined by the ATP III criteria, was 28% in men and 39.6% in women [20]. Our study outcomes are in accordance with these former reports. However, other studies have reported that males have a higher prevalence of MetS than that of females. For example, Tao et al found that the 5-year cumulative incidence of MetS in Beijing adults was 14.22% for males and 7.59% for females [21]; Yang et al revealed that the 5-year cumulative incidence of MetS in Taiwanese adults was 14.95% for males and 9.89% for females [22]. Difference in the findings might be due to a different study design and/or the selected population.

It is well known that MetS represents a cluster of simultaneously occurring metabolic abnormalities. In fact, previous studies demonstrated that RBC and Hb levels clearly increased with the numbers of MetS components [16. 23], and this is demonstrated in our outcomes. It has also been shown that a higher number of MetS components is associated with insulin resistance. Based on the facts that levels of RBC, HCT and Hb are significantly associated with insulin resistance [10, 12, 24], we hypothesize that increased levels of erythrocyte parameters tested in this study may be indicative of the development of insulin resistance.

Several studies have demonstrated an association between RBC levels and MetS, indicating the RBC variable is a potential hematological marker for early detection of MetS [14-16]. Our results revealed that the highest tertiles of RBC were associated with MetS in females, consistent with a recent study [25].The pathogenesis of insulin resistance may, in part, be causative of the association between RBC levels and MetS. Aoki et al reported that insulin can stimulate the proliferation and differentiation of erythropoietic cells by blinding receptors on the cell surface [26]. It was suggested that insulin and

insulin growth factors I and II can promote the proliferation and differentiation of erythroid progenitors in human bone marrow and circulation [27-29]. Alternatively, the relationship between RBC levels and MetS may be a result of iron overload. It was reported that iron overload was associated with insulin resistance [30], and excessive body iron storage interfered with insulin-mediated effects, while bloodletting improved insulin sensitivity [31]. Bozzini et al found that iron overload was strongly associated with obesity and dyslipidemia, and serum ferritin tests would help identify a subgroup of individuals at risk for insulin resistance-associated hepatic iron overload.[32]. Additionally, erythrocyte fatty acids maybe another linking factor between RBC levels and MetS. Novgorodtseva et al found that the development of MetS was accompanied by changes to the composition of erythrocyte fatty acids [33]. Zong et al also demonstrated that erythrocyte fatty acids in the de novo lipogenesis pathway were independently associated with an elevated risk of MetS [34]. Fatty acid composition in erythrocytes may affect insulin sensitivity in individuals with MetS. This may be the underlying mechanism linking insulin resistance to changes in fatty acid composition of RBCs in individuals with MetS [35].

Hb, another important erythrocyte parameter, has been reported to be associated with MetS in both cross-sectional and cohort studies [14, 16-17, 36]. An 8-year follow-up cohort study conducted in Japan detected that the highest and third quartiles of Hb concentration were associated with increased risk of MetS incidence compared to the lowest quartiles of Hb concentration in males, but there was no association observed in females [17]. In general, our findings were consistent with those of the previous reports. In our study, the ORs of MetS increased across the successive tertiles of Hb among males; however, no similar trend was observed among females. The following mechanisms may be regarded as the causes of association between Hb and MetS: Hb is a well-known carrier and buffer of nitric oxide (NO), and can regulate the endothelial function of blood vessels by modulating NO levels in blood [37]. Furthermore, Hb and various compounds of NO modulate the affinity between Hb and oxygen in blood, which can lead to vascular endothelial dysfunction [38]. It has been found that vascular endothelial dysfunction was associated with MetS [39-40]. In addition, Hb plays a key role in regulating sCD40L levels [41], and sCD40L has been shown to participate in thrombus formation and inflammation, which is an independent risk factor for atherosclerosis and MetS [42]. Another possibility linking Hb and MetS may be adiponectin. Previous studies showed that higher Hb levels were closely related to lower adiponectin levels [43-44], and lower levels of adiponectin significantly increased the risk for MetS, respectively. Finally, insulin resistance may also be involved in the

association between Hb and MetS [8, 12].

RDW, a common index of routine blood examination, represents a measure of heterogeneity in the size of circulating erythrocytes. A high RDW index indicates greater heterogeneity in size of circulating erythrocytes in a subject. In this study, males in the highest tertiles of RDW (>13.2%) had a 2.75-fold increased risk for MetS. Multiple groups previously showed that elevated RDW was associated with MetS [45-46]. For instance, Laufer and colleagues demonstrated that RDW ≥14% was independently associated with an increased risk for MetS development [45]; Sanchez-Chaparro and colleagues reported that the highest quartile of RDW (>14%) was remarkably linked with MetS after adjusting for potential confounders [46]. Moreover, a recent study illustrated RDW is a potential metabolic marker for the detection of metabolic diseases [47]. To date, the mechanism of association between RDW and MetS remains unknown; however, chronic inflammation linked to RDW may play an important role. MetS has previously been associated with chronic inflammation [9], and RDW reflects an underlying inflammatory state [13]. Pierce and colleagues have proved that proinflammatory cytokines can inhibit erythropoietin-induced erythrocyte maturation, which may lead to an elevation of RDW [48].

Our study was conducted in the Pearl River Delta region of China, and it may imply that the generalisability of our results is limited to this region. Additionally, participants with a history of cardiovascular diseases, severe liver and kidney dysfunction, tumors, and severe inflammatory diseases were excluded, so our results are not applicable to these subjects.

There were several limitations in this study. First, the present study was designed as a cross-sectional study; therefore, direct causation cannot be concluded from the results. Then, supplementary information about the lifestyle of the subjects was not collected; therefore, these factors, such as smoking, physical exercise and dietary, could not be included in the adjustments of our multivariate logistic regression analyses.

**Conclusions**

In our study, MetS was more prevalent in females than that in males. The association between erythrocyte parameters and MetS differed between sexes, whereby RBC and Hb were identified as the risk factors of MetS in females and Hb and RDW as the risk factors in males. This has important clinical implications for health makers that erythrocyte parameters may serve as effective indices for the early detection of MetS risk and the treatment of MetS on a sex-dependent basis.

**Acknowledgments:** We gratefully acknowledge the staff of local Community Health Service Agencies, for their kind assistance in data collection.

**Contributors:** LLH and PXW conducted the data analyses. LLH, NL, XXW, LYF and XW drafted the manuscript.PXW and DMD finalized the manuscript with input from all authors. All authors contributed to the development of the study framework, interpretation of the results, revisions of successive drafts of the manuscript, and approved the version submitted for publication.

**Funding:** This study was supported by the Guangzhou 121 Talents Program (GZRSH-2014-2048), the Science and Technology Program of Guangzhou (201607010136, 201510010109)and the National Science Foundation of China (81402716).

**Conflicts of Interest:** The authors declare that they have no conflicts of interest.

**Ethical approval:** The study was approved by the Ethics Committee of Guangdong Sociological Society..

**Informed consent:** Informed consent was obtained from all individual participants included in the study.

**Data sharing statement:** This database is first used in this study. The database belongs to our team, and if shared, you need to get their permission.

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**Figure Legends**

**Figure 1**Proportion of metabolic syndrome (MetS) components from zero to five between males and females.

**Figure 2** Prevalence of metabolic syndrome (MetS) in association with the tertiles ofred blood cell (RBC), hematocrit (HCT), hemoglobin (Hb), and red blood cell distribution width (RDW) in males and females, separately.

**Table 1** Characteristics of study subjects with and without metabolic syndrome stratified by sex

| Variables | Male (n=2161) | | | Female (n=2511) | | |
|---|---|---|---|---|---|---|
| | MetS | Non-MetS | *P* | MetS | Non-MetS | *P* |
| MetS status (n, %) | 576 (26.7) | 1585 (73.3) | | 885 (35.2) | 885 (35.2) | |
| Age (years) | 51.39 ± 12.21 | 54.61 ± 13.79 | **<0.001** | 59.78 ± 12.34 | 55.70 ± 12.97 | **<0.001** |
| **Components of MetS** | | | | | | |
| WC (cm) | 89.98 ± 6.79 | 82.40 ± 7.76 | **<0.001** | 85.94 ± 7.21 | 77.59 ± 8.56 | **<0.001** |
| SBP (mmHg) | 134.93 ± 15.20 | 127.57 ± 16.32 | **<0.001** | 136.49 ± 16.42 | 124.74 ± 18.39 | **<0.001** |
| DBP (mmHg) | 89.24 ± 10.47 | 82.93 ±11.09 | **<0.001** | 84.13 ± 10.25 | 78.51 ± 10.53 | **<0.001** |
| TG (mmol/L) | 2.76 ± 1.77 | 1.29 ± 0.91 | **<0.001** | 2.15 ± 1.41 | 1.20 ± 1.87 | **<0.001** |
| HDL-C (mmol/L) | 1.00 ± 0.47 | 1.28 ± 0.44 | **<0.001** | 1.17 ± 0.22 | 1.50 ± 0.34 | **<0.001** |
| FPG (mmol/L) | 5.53 ± 2.01 | 4.87 ± 1.40 | **<0.001** | 5.38 ± 1.86 | 4.71 ± 0.97 | **<0.001** |
| **Erythrocyteparameters** | | | | | | |
| RBC ($\times10^{12}$/L) | 4.99 ± 0.80 | 4.53 ± 0.51 | **<0.001** | 4.55 ± 0.84 | 4.10 ± 0.57 | **<0.001** |
| HCT (%) | 42.27 ± 4.09 | 40.68 ± 3.63 | **<0.001** | 37.35 ± 2.80 | 35.58 ± 2.83 | **<0.001** |
| Hb (g/L) | 147.11 ± 12.57 | 139.02 ± 12.68 | **<0.001** | 129.68 ± 14.45 | 121.50 ± 11.82 | **<0.001** |
| RDW (%) | 13.33 ± 0.96 | 12.87 ± 1.21 | **<0.001** | 13.18 ± 1.90 | 12.88 ± 2.27 | **<0.001** |
| **Liver function parameters** | | | | | | |
| ALT (u/L) | 31.44 ± 18.35 | 26.31 ± 15.52 | **<0.001** | 24.09 ± 13.81 | 21.14 ± 11.79 | **<0.001** |
| AST (u/L) | 26.37 ± 15.87 | 24.80 ± 10.00 | **0.026** | 23.82 ± 8.90 | 23.27 ± 8.63 | 0.129 |
| GGT(u/L) | 48.73 ± 39.88 | 36.04 ± 26.83 | **<0.001** | 32.00 ± 22.79 | 26.12 ± 26.03 | **<0.001** |
| ALB (g/L) | 47.36 ± 3.23 | 47.32 ± 4.07 | 0.820 | 47.48 ± 4.32 | 47.77 ± 12.28 | 0.484 |
| **Other clinical characteristics** | | | | | | |
| BMI (kg/m$^2$) | 25.90 ± 2.67 | 23.61 ± 3.04 | **<0.001** | 25.21 ± 3.05 | 22.85 ± 3.17 | **<0.001** |
| TC (mmol/L) | 4.81 ± 0.95 | 4.73 ± 0.94 | 0.059 | 5.26 ± 1.08 | 5.08 ± 1.02 | **<0.001** |
| LDL-C (mmol/L) | 2.65 ± 0.70 | 2.66 ± 2.06 | 0.885 | 2.95 ± 1.48 | 2.75 ± 1.03 | **<0.001** |
| UA (umol/L) | 415.45 ± 143.27 | 382.19 ± 84.92 | **<0.001** | 340.60 ± 83.08 | 306.95 ± 101.63 | **<0.001** |
| WBC ($\times10^9$/L) | 6.95 ± 1.40 | 6.43 ± 1.40 | **<0.001** | 6.41 ± 1.35 | 5.84 ± 1.31 | **<0.001** |
| PLT ($\times10^9$/L) | 214.70 ± 49.89 | 201.57 ± 52.17 | **<0.001** | 224.04 ± 53.55 | 216.73 ± 52.14 | **0.001** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| HbAIc (%) | 5.79 ± 1.37 | 5.42 ± 0.97 | **<0.001** | 5.64 ± 1.22 | 5.33 ± 0.67 | **<0.001** | |

Data were presented as mean ± SD or *n* (%);MetS, metabolic syndrome; WC, waist circumference;SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C,high-densitylipoprotein cholesterol; FPG, fasting plasma glucose; RBC, red blood cell; HCT, hematocrit; Hb, hemoglobin; RDW, red blood cell distribution width; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; ALB, albumin; BMI, body mass index; TC, total cholesterol;LDL-C, low-density lipoproteincholesterol; UA, uric acid; WBC, white blood cell; PLT, platelet; HbAIc, glycated hemoglobin A1c.

**Table 2** Levels of erythrocyte parameters of study subjects according to number of metabolic syndrome components in males and females, respectively

| Variables | 0 | 1 | 2 | 3 | 4 | 5 | *F* | *P* |
|---|---|---|---|---|---|---|---|---|
| **Male** | | | | | | | | |
| RBC | 4.44 ± 0.53 | 4.55 ± 0.50 | 4.55 ± 0.52 | 4.80 ± 0.54 | 5.31 ± 0.86 | 5.95 ± 1.23 | 87.448 | **<0.001** |
| HCT | 39.96 ± 3.39 | 40.76 ± 3.88 | 41.00 ± 3.38 | 42.12 ± 4.10 | 42.33 ± 4.14 | 44.21 ± 3.01 | 19.799 | **<0.001** |
| Hb | 131.60 ± 12.35 | 138.81 ± 12.86 | 140.71 ± 12.41 | 144.51 ± 11.65 | 151.28 ± 12.87 | 160.04 ± 9.19 | 52.445 | **<0.001** |
| RDW | 12.75 ± 0.82 | 12.83 ± 1.55 | 13.00 ± 0.80 | 13.24 ± 0.86 | 13.41 ± 1.07 | 14.33 ± 1.13 | 20.264 | **<0.001** |
| **Female** | | | | | | | | |
| RBC | 4.03 ± 0.39 | 4.07 ± 0.52 | 4.16 ± 0.54 | 4.45 ± 0.82 | 4.67 ± 0.88 | 4.83 ± 0.78 | 66.453 | **<0.001** |
| HCT | 35.16 ± 2.65 | 35.43 ± 2.78 | 35.91 ± 2.91 | 37.07 ± 2.81 | 37.74 ± 2.79 | 37.96 ± 2.36 | 52.237 | **<0.001** |
| Hb | 119.70 ± 11.54 | 121.28 ± 11.79 | 122.49 ± 11.88 | 128.26 ± 14.04 | 130.04 ± 14.35 | 139.61 ± 14.46 | 59.262 | **<0.001** |
| RDW | 12.71 ± 2.10 | 12.74 ± 1.40 | 13.07 ± 2.87 | 13.11 ± 1.39 | 13.25 ± 2.70 | 13.38 ± 1.13 | 4.493 | **<0.001** |

RBC, red blood cell; HCT, hematocrit; Hb, hemoglobin; RDW, red blood cell distribution width.

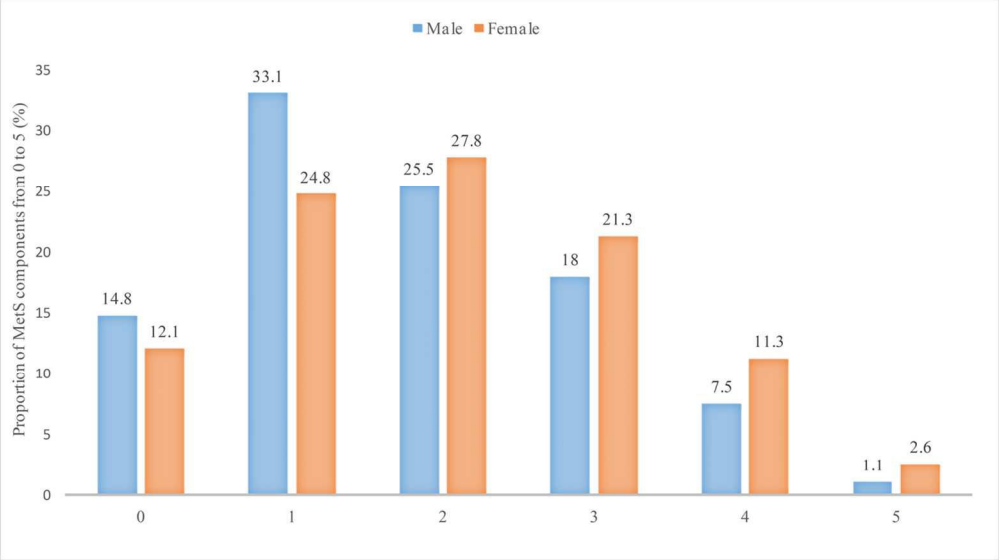
**Table 3** Odds ratios of erythrocyte parameters associated with metabolic syndromestratified by sex

| Variables | Male | | Female | |
|---|---|---|---|---|
| | *OR (95% CI)* | *P* | *OR (95% CI)* | P |
| **Age** | 0.999 (0.986~1.013) | 0.930 | 1.012 (0.998~1.025) | 0.088 |
| **WC** | 1.157 (1.121~1.194) | **<0.001** | 1.130 (1.103~1.158) | **<0.001** |
| **SBP** | 1.025 (1.012~1.039) | **<0.001** | 1.041 (1.031~1.051) | **<0.001** |

| | | | | |
|---|---|---|---|---|
| **DBP** | 1.025 (1.006~1.045) | **0.011** | 1.030 (1.013~1.047) | **0.001** |
| **TG** | 3.240 (2.697~3.893) | **<0.001** | 1.518 (1.269~1.817) | **<0.001** |
| **HDL-C** | 0.026 (0.012~0.054) | **<0.001** | 0.001 (0.001~0.003) | **<0.001** |
| **FPG** | 1.725 (1.410~2.111) | **<0.001** | 2.221 (1.836~2.687) | **<0.001** |
| **ALT** | 0.996 (0.980~1.012) | 0.620 | 1.002 (0.990~1.014) | 0.757 |
| **AST** | 1.016 (0.988~1.045) | 0.260 | | |
| **GGT** | 1.001 (0.997~1.006) | 0.492 | 1.005 (1.000~1.010) | **0.064** |
| **BMI** | 0.976 (0.907~1.049) | 0.506 | 1.015 (0.958~1.076) | 0.620 |
| **TC** | | | 1.243 (1.061~1.455) | **0.007** |
| **LDL-C** | | | 0.992 (0.903~1.090) | 0.867 |
| **UA** | 1.001 (0.999~1.003) | 0.291 | 1.001 (0.999~1.002) | 0.303 |
| **WBC** | 1.044 (0.935~1.165) | 0.447 | 1.063 (0.959~1.178) | 0.248 |
| **PLT** | 1.002 (0.999~1.005) | 0.202 | 1.001 (0.998~1.003) | 0.639 |
| **HbAIc** | 0.856 (0.649~1.130) | 0.273 | 0.747 (0.572~0.976) | **0.032** |
| **RBC** | | | | |
| Q1 | Reference | | Reference | |
| Q2 | 0.940 (0.613~1.443) | 0.779 | 1.070 (0.743~1.541) | 0.716 |
| Q3 | 1.207 (0.771~1.889) | 0.410 | 1.718 (1.173~2.515) | **0.005** |
| **HCT** | | | | |
| Q1 | Reference | | Reference | |
| Q2 | 0.771 (0.482~1.234) | 0.279 | 1.419 (0.933~2.159) | 0.102 |
| Q3 | 0.968 (0.606~1.547) | 0.893 | 1.407 (0.896~2.208) | 0.138 |
| **Hb** | | | | |
| Q1 | Reference | | Reference | |
| Q2 | 1.921 (1.170~3.151) | **0.010** | 1.538 (1.008~2.348) | **0.046** |
| Q3 | 1.992 (1.198~3.312) | **0.008** | 1.665 (1.075~2.578) | **0.022** |
| **RDW** | | | | |
| Q1 | Reference | | Reference | |
| Q2 | 1.114 (0.757~1.639) | 0.583 | 0.787 (0.571~1.085) | 0.144 |

| | | | | |
|---|---|---|---|---|
| Q3 | 2.725 (1.915~3.878) | **<0.001** | 1.057 (0.753~1.484) | 0.750 |

OR, odds ratio; CI, confidence interval; Statistical analysis bybinary logistic regression with adjustments for potential confounders (the statistically significant variables in table 1, Male: adjusted for age, WC [waist circumference], SBP [systolic blood pressure], DBP [diastolic blood pressure], TG [triglyceride], HDL-C [high-densitylipoprotein cholesterol], FPG [fasting plasma glucose], ALT [alanine transaminase], AST [aspartate aminotransferase], GGT [γ-glutamyl transferase],BMI [body mass index], UA [uric acid], WBC [white blood cell], PLT [platelet] and HbAIc [glycated hemoglobin A1c]; Female:adjusted for age, WC, SBP, DBP, TG, HDL-C,FPG, ALT, GGT,BMI, TC [total cholesterol], LDL-C [low-density lipoproteincholesterol],, UA, WBC, PLT and HbAIc); RBC, red blood cell; HCT, hematocrit; Hb, hemoglobin; RDW, red blood cell distribution width.

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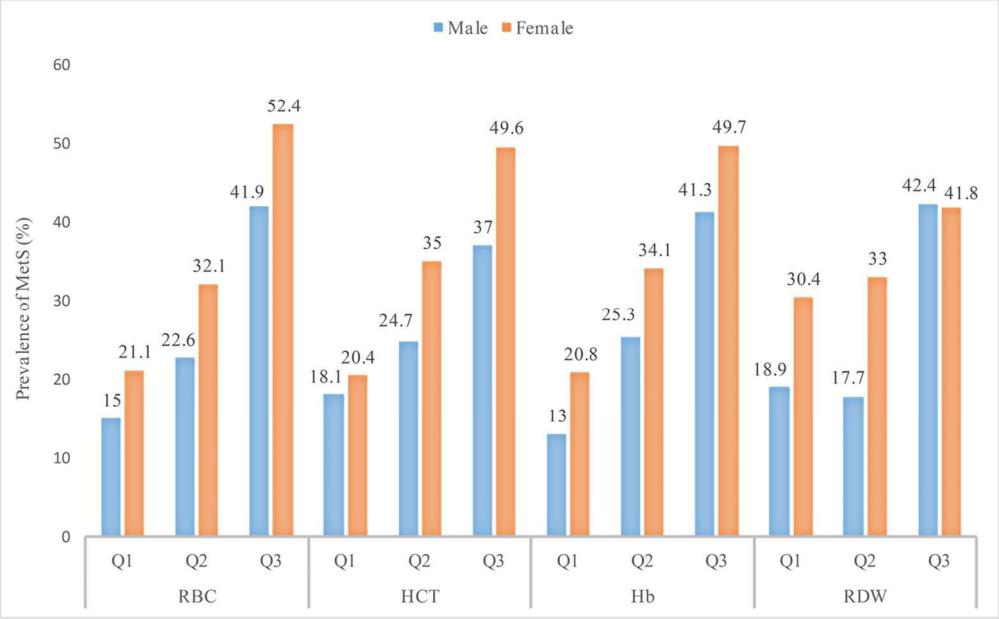


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