# Sex based levels of C-reactive protein and white blood cell count in subjects with metabolic syndrome: Isfahan Healthy Heart Program

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**Background:** C-reactive protein (CRP) and white blood cell (WBC) are proinflammatory markers. They are major pathophysiological for the development of metabolic syndrome (MetS). This study aimed to address the independent associations between MetS and WBC counts and serum CRP levels and evaluation of their magnitude in relation to the MetS, based on the sex in the Iranian adults. **Materials and Methods:** In this cross-sectional study, subjects who met the MetS criteria, based on the Adult Treatment Panel III were selected from the Isfahan Healthy Heart Program database. A questionnaire containing the demographic data, weight, height, waist, and hip circumference of the respondents was completed for each person. Blood pressure was measured and the anthropometric measurements were done, and fasting blood samples were taken for 2 h postload plasma glucose (2 hpp). Serum [total, high-density lipoprotein (HDL), and low-density lipoprotein] levels of cholesterol, triglyceride, and CRP as well as WBC counts were determined. The univariate analyses were carried out to assess the relation between the CRP levels, WBC counts with the MetS in both sexes the. **Results:** In men with the abdominal obesity, the higher levels of WBC count, high serum triglyceride and blood glucose levels, a low serum HDL level, and raised systolic and diastolic blood pressure were observed. However, the higher serum CRP levels were only observed in those with the low serum HDL-cholesterol levels. The mean values of the WBC counts were statistically different between the men with and without MetS, but the mean values of the CRP levels were similar between the two groups. In women, the mean values of WBC count and CRP levels were statistically different in the subjects with and without a MetS components (except for the low serum HDL levels and high diastolic blood pressure for the WBC measures and abdominal obesity for the CRP measures) and for those with and without MetS. The age and smoking adjusted changes in the CRP levels and WBC counts correlated with the number of Mets components in the women. **Conclusion:** The findings of this study suggest substantial implications for the prevention and management of the MetS and atherosclerotic diseases, as these involve the suppression of inflammatory conditions rather than the incitement of anti-inflammatory conditions.

**Key words:** C-reactive protein level, metabolic syndrome, white blood cell count

## INTRODUCTION

Metabolic syndrome (MetS) is conceptualized as a clustering of risk factors, including insulin resistance, dyslipidemia, central adiposity, and high blood pressure that increase the risk of cardiovascular disease and type 2 diabetes mellitus. The combination of these findings defines the MetS.[1,2] There is global agreement that this risk factors gathering increase the risk of cardiovascular disease, and metabolic diseases, such as diabetes and thus has made it a serious public health problem.[3] In fact, numerous studies have shown people with the MetS are more likely to die prematurely and that they are at the greater risk of developing diabetes mellitus and cardiovascular disease.[4,5]

Inflammation is a major pathophysiological factor for the MetS development. Some evidences are available concerning the association between the appearance of MetS and chronic inflammatory response, characterized by the abnormal cytokine production and the activations of inflammatory signaling pathways.[6,7] Furthermore, some inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin-6 are in associated with the MetS and its components in different settings.[6-13] Moreover, there is a proven association between the increased white

blood cell (WBC) count as a biological marker of systemic and the components of the MetS.[14,15]

Nevertheless, there are few studies examining sex-based associations between the CRP level and WBC count as pro-inflammatory markers and the MetS, especially in our population. Indeed, other published findings achieved from small size populations. Therefore, this study aimed to investigate the independent associations between the MetS and WBC count and serum CRP levels in both sexes and evaluation of their magnitude in relation to the MetS in the Iranian adults.

## MATERIALS AND METHODS

### Study population
The Isfahan Healthy Heart Program is a comprehensive integrated community-based action-oriented study with a reference community has been conducted by the Isfahan Cardiovascular Research Institute since 2000 and completed in 2007 in Isfahan.[16,17] A random independent sample of adults was selected by the multistage cluster sampling. The effect of confounding was addressed by using the random, stratified household sampling, based on age and sex groups. The participants were more than 19 years old. Finally, 4719 subjects with MetS entered in our study. The samples underwent a 30-min interview by well-trained examiners to complete the validated questionnaires containing questions on demography, socioeconomic status, smoking behavior, physical activity, nutritional habits, and other risk profiles. Informed consent was obtained from all subjects prior to their participation in this study. This study was approved by the Ethical Committee of the Isfahan University of Medical Sciences. Isfahan Healthy Heart Program (IHHP) was covered under the institutional review board protocol FW A00008578.

### Data collection
Information on the sociodemographic factors and self-reported medical history were obtained by interview. Anthropometric measurements, including height, weight, and waist and hip circumferences were taken with the subjects wearing light clothing by well-trained examiners. Waist circumference was measured to the nearest 0.1 cm in the horizontal plane at the high point of the iliac crest during minimal respiration.[17] Blood pressure was measured with a mercury sphygmomanometer using right arms, in a sitting position, after a 5-min rest. Systolic and diastolic blood pressures were recorded twice and the averages were used for the data analysis. Blood samples were drawn from anantecubital vein after an 8-12 h overnight fast. Samples were stored at −20°C until required for the biochemical assays. Fasting venous blood samples were obtained from the antecubital vein between 08:00 and

09:30 am. Blood samples were centrifuged for 10 min at 906 g within 30 min of collection. Sera were analyzed for the total cholesterol (TC), high-density lipoprotein (HDL), triglycerides (TG), and fasting blood glucose (FBG). Low-density lipoprotein-cholesterol (LDL) was calculated by Friedwald equation when TG was less than 400 mg/dL.[18] TC was measured using enzymatic colorimetric methods. HDL-C was determined after dextran sulphate-magnesium chloride precipitation of HDL. The serum CRP levels were measured with the same autoanalyzer. The assay (Pars Azmoun) had a limit of detection 0.05 mg/L and an upper limit of 160 mg/L. WBC count was determined using the sysmex.[16,17] All the tests were performed in the Central Laboratory of the Isfahan Cardiovascular Research Center using the autoanalyzer ELAN (Ependorf 2000). For quality-control measures, this laboratory meets the criteria of the national standard laboratory (a WHO collaborating centre in Tehran).

### MetS definition
The ATPIII definition of MetS was met when three or more of the following criteria were present: Waist circumference ≥102 in cm the men and 88 cm in the women; HDL ≤40 mg/dL in the men and 50 mg/dL in the women or specific treatment for this lipid abnormality; TG ≥150 mg/dL or specific treatment for this lipid abnormality; systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or treatment of previously diagnosed hypertension; and fasting glucose ≥100 mg/dL.[14]

### Statistical analyses
Results were reported as mean ± standard deviation for the quantitative variables and percentages for the categorical variables. The groups were compared using the *t-test* for the continuous variables and the Chi-square test for the categorical variables. *P* values of 0.05 or less were considered significant. All the statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows.

The associations between the serum CRP levels and WBC count with the MetS components were examined with the logistic regression analysis. The significance level was set at $P > 0.05$.

## RESULTS

The personal and clinical characteristics of the study subjects are presented in Table 1. Systolic and diastolic blood pressures were significantly higher in the men than in the women. Serum CRP and blood sugar levels were similar between the two genders. Levels of triglyceride and WBC counts were higher in the men compared with the women. Conversely, LDL cholesterol levels were higher in

## Table 1: Demographic and clinical characteristics of the study subjects by sex

| Characteristics | Total (*n*, %) | Men (*n*, %) | Women (*n*, %) | *P* value |
|---|---|---|---|---|
| Age | | | | |
|   19-24 years | 924 (19.6) | 459 (19.7) | 465 (19.5) | 0.987 |
|   25-34 years | 1439 (30.5) | 718 (30.9) | 721 (30.2) | |
|   35-44 years | 923 (19.6) | 447 (19.2) | 476 (19.9) | |
|   45-54 years | 650 (13.8) | 322 (13.8) | 328 (13.7) | |
|   55-64 years | 356 (7.6) | 173 (7.4) | 183 (7.7) | |
|   ≥65 years | 420 (8.9) | 206 (8.9) | 214 (9.0) | |
| Mean age (year) | 38.54±15.27 | 38.48±15.45 | 38.61±15.10 | 0.775 |
| Systolic blood pressure (mm Hg) | 112.91±18.27 | 115.75±17.31 | 110.14±18.76. | 0.000 |
| Diastolic blood pressure (mm Hg) | 74.43±11.06 | 76.13±10.50 | 72.76±11.34 | 0.000 |
| Fasting blood glucose (mg/dL) | 101.25±32.89 | 100.61±34.53 | 101.87±31.23 | 0.209 |
| Triglyceride (mg/dL) | 142.66±105.95 | 154.20±117.82 | 91.68±1.89 | 0.000 |
| HDL-cholesterol (mg/dL) | 43.46±10.29 | 40.46±9.11 | 46.38±10.55 | 0.000 |
| LDL-cholesterol (mg/dL) | 117.90±33.03 | 115.57±32.47 | 120.16±33.42 | 0.000 |
| White blood cell (mg/dL) | 6704.55±1640.66 | 6766.08±1608.57 | 6642.49±1670.48 | 0.014 |
| CRP (mg/dL) | 2.66±2.23 | 2.70±2.28 | 2.62±2.17 | 0.224 |
| Metabolic syndrome | 982 (21.1) | 365 (16.0) | 617 (26.1) | 0.000 |

Data are presented as mean±standard deviation or number (%); CRP=C-reactive protein; HDL=High-density lipoprotein; LDL=Low-density lipoprotein

## Table 2: Metabolic syndrome components and mean value of white blood cell and C-reactive protein in both sexes

| Biomarkers | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Number (%) | WBC (103/uL) | CRP (mg/L) | Number (%) | WBC (103/uL) | CRP (mg/L) |
| Abdominal obesity | | | | | | |
|   Present | 292 (12.5) | 7259.69±1598.82 | 2.93±2.45 | 1183 (49.5) | 6856.69±1751.81 | 2.72±2.45 |
|   Absent | 1921 (82.6) | 6689.95±1608.99 | 2.68±2.29 | 1071 (44.8) | 6424.79±1567.80 | 2.56±1.89 |
|   *P* value | - | 0.000 | 0.105 | - | 0.000 | 0.084 |
| Low HDL-cholesterol | | | | | | |
|   Present | 1146 (49.2) | 6926.82±1597.30 | 2.82±2.36 | 1519 (63.5) | 6683.36±1684.34 | 2.54±2.19 |
|   Absent | 1139 (48.9) | 6612.28±1611.62 | 2.58±2.19 | 832 (34.8) | 6572.76±1643.22 | 2.76±2.14 |
|   *P* value | - | 0.000 | 0.014 | - | 0.146 | 0.027 |
| High triglyceride | | | | | | |
|   Present | 851 (36.6) | 7108.00±1633.22 | 2.75±2.10 | 648 (27.1) | 6978.69±1692.65 | 2.88±2.68 |
|   Absent | 1431 (61.5) | 6554.02±1551.98 | 2.68±2.39 | 1711 (71.5) | 6516.34±1644.42 | 2.53±1.95 |
|   *P* value | - | 0.000 | 0.501 | - | 0.000 | 0.001 |
| High glucose | | | | | | |
|   Present | 427 (18.3) | 7016.88±1627.66 | 2.85±2.02 | 558 (23.3) | 6988.33±1932.90 | 2.71±2.09 |
|   Absent | 1674 (71.9) | 6701.49±1605.03 | 2.63±2.33 | 1621 (67.8) | 6502.69±1541.60 | 2.50±1.86 |
|   *P* value | - | 0.001 | 0.090 | - | 0.000 | 0.033 |
| Systole blood pressure | | | | | | |
|   Present | 439 (18.9) | 7000.00±1501.47 | 2.63±1.97 | 359 (15.0) | 6908.78±1916.21 | 2.97±3.01 |
|   Absent | 1809 (77.7) | 6708.80±1634.34 | 2.73±2.38 | 1934 (80.8) | 6598.20±1627.98 | 2.58±2.01 |
|   *P* value | - | 0.001 | 0.408 | - | 0.002 | 0.004 |
| Diastole blood pressure | | | | | | |
|   Present | 386 (16.6) | 7030.67±1655.61 | 2.61±2.09 | 320 (13.4) | 6820.65±1783.43 | 2.90±3.15 |
|   Absent | 1861 (80.0) | 6711.35±1600.23 | 2.74±2.35 | 1970 (82.4) | 6618.01±1657.77 | 2.60±1.99 |
|   *P* value | - | 0.001 | 0.329 | - | 0.062 | 0.036 |
| Raised blood pressure | | | | | | |
|   Present | 606 (26.0) | 6983.89±1579.91 | 2.63±2.03 | 534 (22.3) | 6859.44±1920.59 | 2.89±2.78 |
|   Absent | 1641 (70.5) | 6685.32±1618.96 | 2.74±2.39 | 1756 (73.4) | 6581.27±1590.49 | 2.57±1.98 |
|   *P* value | - | 0.000 | 0.321 | - | 0.002 | 0.005 |
| Metabolic syndrome | | | | | | |
|   Present | 365 (15.7) | 7259.04±1512.38 | 2.87±2.31 | 617 (25.8) | 6963.25±1802.11 | 2.88±2.73 |
|   Absent | 1921 (82.6) | 6673.78±1612.28 | 2.67±2.29 | 1746 (73.0) | 6531.13±1607.84 | 2.53±1.94 |
|   *P* value | - | 0.000 | 0.148 | - | 0.000 | 0.001 |

CRP=C-reactive protein; HDL=High-density lipoprotein; WBC=White blood cell

the women. Totally, the overall prevalence of the MetS was significantly higher in the women.

Table 2 shows the mean values of CRP levels and WBC counts, based on the presence and absence of each MetS components and according to the presence and absence of MetS in the men. In men, with the abdominal obesity a significantly higher level of WBC counts, high serum triglyceride and blood glucose levels and, low HDL-cholesterol levels, and raised systolic and diastolic blood pressures were observed. However, significantly higher serum CRP levels were only observed in those with the low HDL-cholesterol levels. The mean values of WBC counts were statistically different between the men with and without the MetS, but the mean values of CRP levels were similar between the two groups.

In women [Table 3], the mean values of WBC counts and CRP levels were statistically different in the subjects with and without a MetS component (except for the low HDL-cholesterol levels and high diastolic blood pressure for the WBC measures and abdominal obesity for the CRP measures) and for those with and without the MetS.

Furthermore, Table 3 hows the association between the CRP levels and WBC counts with the presence of the metabolic syndrome components. After adjustment for the age and smoking, significant relation was found between the number of the MetS components and WBC counts in both sexes. Association between the CRP levels and the number of the MetS components was insignificant.

## DISCUSSION

This study aimed to identify the associations between the WBC counts and the serum CRP levels with the MetS in the adult Iranian population. The results showed that WBC counts were associated with the MetS in both men and women. However, the CRP levels were only associated with the MetS in the women. WBC counts were not significantly associated with the low HDL cholesterol levels as well as the increased diastolic blood pressure in the men, but this association was confirmed between different components of the MetS and WBC counts in the men. This result supports the findings of previous studies concerning a linear independent association between the WBC count and the risk of the MetS.[19,20] However, in other studies; finding was not specified in men or women. Overall, it seems that an increased WBC count may exacerbate insulin resistance and lead to the MetS and this pathway might be different in the two genders in various populations.

CRP is a sensitive marker of systemic inflammation which is produced by the liver.[14] Various studies have reported a linear association between the CRP levels and the metabolic disorders, including insulin resistance, the MetS, and the components of MetS.[21,22] In the Finnish Diabetes Prevention Study, CRP introduced as the best immunological predictor for the progression from impaired glucose tolerance to overt type 2 diabetes.[23] In our study, women participants with MetS were found to have significantly higher CRP levels than those without. On the contrary, we could not observe an independent association between the CRP level and MetS in the whole study population. In men, CRP did not increase significantly as a risk factor for the development of the MetS, while in the women; CRP was in association with the MetS. This finding was totally inconsistent with the study of Ryu *et al.*[23] To the best of our own knowledge, there is presently no study regarding the association between the inflammation and the MetS with sex. In this study, some baseline factors differed between the men and women, and it is likely that another set of factors related to inflammation influence this situation, such as cyclical hormonal changes associated with the menstrual cycle and subclinical autoimmune reactions.[23] Saltevo *et al.*, showed that the levels of proinflammatory markers of

**Table 3: Univariate analyses with between white blood cell and C-reactive protein with number of metabolic syndrome components after adjusting by age and smoking**

| Sex | Number of MetS components | WBC | | | CRP | | |
|---|---|---|---|---|---|---|---|
| | | Mean | Se | *P* value | Mean | Se | *P* value |
| Women | 0 | 6360.317[a] | 185.131 | 0.000 | 2.685[c] | 0.247 | 0.005 |
| | 1 | 6501.961[a] | 176.661 | | 2.370[c] | 0.235 | |
| | 2 | 6947.218[a] | 178.819 | | 2.296[c] | 0.238 | |
| | 3 | 7112.109[a] | 187.667 | | 2.276[c] | 0.249 | |
| | MetS ≥4 | 7687.177[a] | 207.706 | | 2.785[c] | 0.279 | |
| Men | 0 | 6594.448[b] | 67.081 | 0.000 | 2.912[c] | 0.096 | 0.107 |
| | 1 | 6752.981[b] | 64.265 | | 2.659[d] | 0.092 | |
| | 2 | 7249.343[b] | 70.918 | | 2.589[d] | 0.103 | |
| | 3 | 7515.865[b] | 107.807 | | 2.853[d] | 0.157 | |
| | MetS ≥4 | 7485.372[b] | 154.311 | | 2.857[d] | 0.225 | |

[a]Covariates appearing in the model are evaluated at the following values: Age (years) = 38.74; [b]Covariates appearing in the model are evaluated at the following values: Age (years) = 38.47; [c]Covariates appearing in the model are evaluated at the following values: Age (years) = 38.28; [d]Covariates appearing in the model are evaluated at the following values: Age (years) = 38.29; CRP=C-reactive protein; MetS=Metabolic syndrome; WBC=White blood cell

CRP and interlukine-1, were significantly higher among the women with the MetS, rather than the men with the MetS, independently of the definition used International Diabetes Federation and National Cholesterol Education Program-Third Adult Treatment Panel. In contrast, another study showed that there was no difference between the men and the women without the MetS regarding the serum interlukine-1and CRP levels.[25] In this context, a recent meta-analysis has demonstrated that the high testosterone levels are associated with the high risk of type 2 diabetes in women, but with low risk in men.[26] High concentrations of sex hormone-binding-globulin are associated with the decreased risk of diabetes, particularly in the postmenopausal women.[27] Overall, although available data on the effects of gender relationships between the serum CRP levels and the MetS or atherosclerosis have been reported;[28] further prospective studies are required to confirm the contribution of CRP and other inflammatory markers to the development of the MetS. If this were confirmed, it would have substantial implications for the prevention and management of the MetS and atherosclerotic diseases, as these involve the suppression of inflammatory conditions rather than the incitement of anti-inflammatory conditions.

### Limitation

The main limitation of this study was its cross-sectional design. In addition, this study could not show the temporal ordering of the association between the CRP levels, WBC counts and the MetS. Further longitudinal investigations are needed to confirm these associations.

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