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Research Article

The Association Between Leukocyte Parameters and Metabolic Syndrome: A Systematic Review and Meta-Analysis

Ting-yi Pu[1], Man Cui[1], Hao-di Li[2], Xi Gao[3], Ding-hua Liu[1, *]

[1]Department of Clinical Laboratory, University-Town Hospital of Chongqing Medical University, Chongqing, China

[2]College of Laboratory Medicine, Chongqing Medical University, Chongqing, China

[3]Department of Traditional Chinese Medicine, University-Town Hospital of Chongqing Medical University, Chongqing, China

Abstract

Background: Metabolic syndrome (MetS) is a cluster of disorders with a high incidence which can lead to the development of type 2 diabetes mellitus and cardiovascular disease. Chronic low-grade inflammation has been implicated in the development of metabolic syndrome. Inflammatory markers such as C-reactive protein have been proved to be associated with MetS, but they are often used in disease diagnosis rather than in routine health screening. Instead, leukocyte is a convenient inflammatory marker. However, the association between leukocyte-related parameters and MetS remains unclear. Therefore, we aimed to perform a systematic review and meta-analysis to evaluate the association between leukocyte parameters and MetS. *Materials and Methods*: PubMed, EMBASE, Cochrane, and Web of Science were searched for articles published from September 2012 to September 2022 for studies on the association of leukocyte with MetS patients. Outcome data were extracted and the standardized mean difference (SMD) and 95% confidence interval (CI) were calculated. STATA software version 16.0 was utilized to conduct meta-analyses and assess publication bias. *Results*: A literature search of all major databases retrieved 2661 studies. After screening, 11 studies were analyzed including a total of 13301 MetS patients. Pooled analysis showed that elevated leukocyte level was significantly associated with MetS (SMD = 0.31, 95% CI (0.23-0.38), Z = 8.07, P <0.001). Conclusion: Elevated leukocyte level may be a potentially useful clinical marker for predicting the possibility of developing MetS in healthy populations.

Keywords

Metabolic Syndrome, Inflammation, Leukocyte, Meta-Analysis

1. Introduction

Metabolic syndrome (MetS) is a cluster of disorders related to abdominal obesity, insulin resistance, hypertension, and dyslipidemia [1, 2]. These conditions can lead to the development of type 2 diabetes mellitus and cardiovascular disease [2]. The prevalence of MetS is increasing worldwide due to changes in diet and lifestyle, making it a global public health concern [3-5].

Chronic low-grade inflammation is thought to be related to

*Corresponding author: dinghualiu@cqmu.edu.cn (Ding-hua Liu)

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the development of insulin resistance and atherogenesis [6, 7]. Some studies have revealed significant associations between inflammation and type 2 diabetes mellitus, cardiovascular disease, insulin resistance, and dyslipidemia, while other studies have implied that chronic inflammation may lead to obesity and glucose intolerance [7, 8].

Inflammatory markers such as C-reactive protein have been found to be associated with MetS [9], but they are often applied in disease diagnosis rather than in routine health examination. Leukocyte-related parameters, as a group of conventional and simple indicators whose applications occur in all medical situations including health examination, have also been sought to correlate with MetS [10, 11]. However, the exact relationship between leukocyte-related parameters and MetS has not been established due to lack of statistical power of the individual studies. Therefore, we conducted a systematic review and meta-analysis aiming to assess the association between leukocyte-related parameters and MetS.

2. Materials and Methods

2.1. Search Strategy and Study Selection

Two authors conducted computerized searches of 4 public databases (PubMed, EMBASE, Cochrane, and Web of Science), from September 2012 to September 2022. Relevant studies were identified by using different combinations of medical subject headings and text words as follows: metabolic syndrome, leukocyte, neutrophil, lymphocyte, monocyte, and neutrophil to lymphocyte ratio. The search results were limited to "human" and only English articles were used. Unpublished studies and non-original articles were not searched. Inclusion criteria were as follows: studies that compared leukocyte, neutrophil, lymphocyte, monocyte, or neutrophil to lymphocyte ratio (NLR) between MetS patients and healthy controls; studies that reported accessible data, such as number of cases, mean, and standard deviation, for both MetS patients and control participants. While studies were excluded if MetS patients combined with other diseases or lack of control group.

2.2. Data Extraction and Quality Assessment

Other two authors independently reviewed eligible studies and fulfilled data extraction. Data on publication year and country, first author, study design, sample size, characteristics of the population studied (number, gender, the diagnostic criteria for MetS etc.), information of controls and outcomes were extracted. Disagreements were resolved by consensus.

The methodological quality of included studies was scored using an 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ). Each item was scored '0' if the answer was 'NO' or 'UNCLEAR', and '1' if the answer was 'YES'. The article quality was assessed as follows: low quality = 0–3; moderate quality = 4–7; high quality = 8–11.

2.3. Statistical Analysis

Analyses were performed with STATA statistical software version 16.0 (College Station, TX). The individual effect size, i.e., the mean difference in leukocyte count between MetS and healthy controls, was calculated as the standardized mean difference (SMD) and 95% confidence interval (CI). Heterogeneity between studies was assessed using the Q-test with $P < 0.05$ and $I2 > 50\%$ as statistical significance. The randomized-effects model was applied if heterogeneity was detected with $P < 0.05$ and $I2 > 50\%$; otherwise, the fixed-effects model was used. Sensitivity analysis was conducted by sequentially omitting one study at a time. Subgroup analysis was also conducted according to gender, country, and diagnostic criteria. Publication bias was assessed visually using the Begg's test and Egger's test $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study Selection

A total of 2661 studies were retrieved from the four public databases. After title and abstract review, 2226 studies were eliminated. Then 41 studies were excluded for being conference abstracts, letters, case reports, systematic reviews, meta-analyses, or studies involving MetS patients with other diseases, or lack of control subjects. Finally, eleven studies were included in the present study [12-22]. The specific selection process is shown in the flowchart (Figure 1).

3.2. Study Characteristics

The main characteristics of the 11 studies are depicted in Table 1. These articles included 13301 MetS patients and 31799 healthy controls. The age of MetS patients ranged from 38 to 75. The number of subjects included in MetS group and healthy control group varied from 70 to 4652 and 71 to 8480, respectively, with the respective leukocyte count ranging from 5.74 to 7.96 in MetS patients and 5.32 to 7.58 in healthy controls. Detailed results are displayed in Table 2. Among the 11 studies, four were conducted in China, three in Turkey, two in Korea, and two in Iran. All of them were cross-sectional studies. The diagnostic criteria of NCEP ATPIII were used to define eight studies, IDF criteria were used to define two studies, and the Joint statement 2009 criteria were used to define one study. All 11 studies provided data on leukocyte count. Three articles provided data on neutrophil count and lymphocyte count, two articles provided data on monocyte count, and none of the studies illustrated the data on NLR.

3.3. Quality Assessment

The AHRQ scores of the included studies varied from 7 to 8, with 6 studies [12, 13, 15, 19, 20, 22] being of moder-

ate-quality and 5 studies [14, 16-18, 21] being of high-quality.

3.4. Meta-Analysis

As shown in Figure 2, the data of all the 11 studies were assessed as statistically significant heterogeneity (P<0.001, I2=88.9%), and were analyzed by random-effects model. Leukocyte level in MetS patients was significantly higher than healthy controls (SMD = 0.31, 95% CI (0.23-0.38), Z = 8.07, P <0.001).

3.5. Subgroup Analysis

The 11 studies were divided into three subgroups based on gender, country, and diagnostic criteria. As shown in Figure 3-A, subgroup analyses showed that the level of leukocyte in males was higher than in females (SMD = 0.34, 95% CI (0.28-0.40), Z = 11.15, P < 0.001). As shown in Figure 3-B, subgroup analyses showed statistically significant heterogeneity according to studies from China, Iran, Korea, and Turkey (SMD = 0.31, 95% CI (0.23-0.38), Z = 8.07, P <0.001). The results revealed that Chinese MetS patients had higher level of leukocyte than those from other countries. As shown in Figure 3-C, subgroup analyses showed statistically significant heterogeneity according to studies diagnosed by NCEP ATP III, IDF, and the Joint Statement 2009 (SMD = 0.31, 95% CI (0.23-0.38), Z = 8.07, P <0.001). The results presented that MetS patients diagnosed by NCEP ATP III had higher level of leukocyte than those diagnosed by IDF or the Joint Statement 2009.

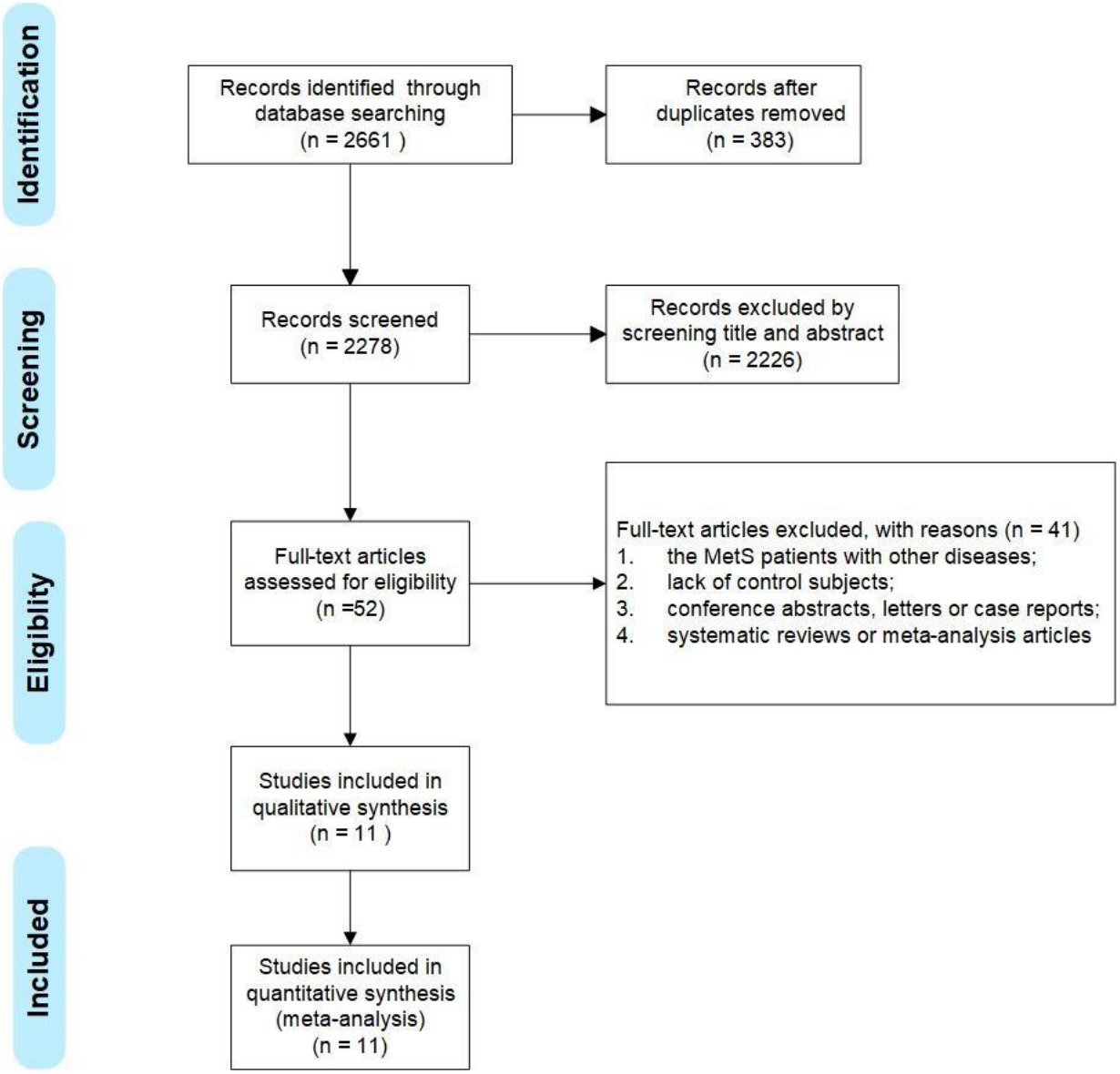


Figure 1. *Flow diagram of literature search.*

Table 1. *Anthropometric, metabolic, and hormonal data of the Mets patients.*

Study	Country	Age (year)	WC (cm)	Blood Pressure (mmHg)	HDL (mg/dL)	TG (mg/dL)	FBG (mg/dL)	Diagnose criteria	Quality score
Chan-Hee Jung 2013	Korea	50.6 ±9.6	NA	120.2 ±14.5/ 78.9 ±10.2	52.0 ±12.7	NA	98.3 ±21.2	NCEP ATPIII	7
Eyup Buyukkaya 2014	Turkey	48 ±10	99 ±11	135 ±18/ 85 ±10	37.12 ±8.89	205.55 ±95.69	110.46 ±25.77	NCEP ATP III	7
Haixia Liu 2014	China	70.1 ±4.6	NA	143.2 ±18.8/ 78.2 ±11.3	50.4 ±12.2	164.9 ±68.7	111.1 ±27.6	NCEP ATPIII	8
Ali Maleki 2014	Iran	55.51 ±10.88	98.26 ±10.14	136.26 ±20.16/ 83.51 ±12.06	40.46 ±5.73	221.94 ±134.67	123.59 ±53.12	NCEP ATPIII	7
Chun Pei 2015 (male)	China	65.1 ±5.4	90.8 ±7.5	138.1 ±17.1/ 81.1 ±11.0	41.3 ±10.5	179.3 ±73.3	112.3 ±30.9	Joint statement 2009	8
Chun Pei 2015 (female)	China	64.5 ±4.9	82.5 ±7.5	139.8 ±17.6/ 78.3 ±10.5	48.9 ±11.7	179.3 ±73.3	108.4 ±25.0	Joint statement 2009	8
Chulwoo Rhee 2015	Korea	NA	NA	NA	NA	NA	NA	NCEP ATPIII	8
Mehmet Kadri Akboga 2015	Turkey	58.9 ±10.8	109.7 ±12.4	NA	NA	NA	NA	NCEP ATP III	8
Jamal Ahmadzadeh 2017	Iran	41.42 ±9.96	103.40 ±7.27	131.92 ±15.65/ 83.53 ±10.29	NA	NA	99.20 ±27.28	IDF	7
Ali Ugur Uslu 2017	Turkey	47.0 ±13.5	NA	NA	NA	NA	93.30 ±14.90	NCEP ATP III	7
Xue-Jiao Yang 2020	China	NA	NA	NA	NA	NA	NA	NCEP ATPIII	8
Tong Chen 2020 (male)	China	57.2 ±10.5	97.38 ±6.22	140.88 ±14.29/ 144.73 ±18.47	46.40 ±9.67	NA	NA	IDF	7
Tong Chen 2020 (female)	China	60.7 ±10.0	89.77 ±6.88	89.16 ±9.04/ 85.52 ±9.15	52.98 ±11.60	NA	NA	IDF	7

* WC = waist circumference, HDL = high-density lipoprotein, TG = triglyceride, FPG = fasting blood glucose, NA = not accessed.

Table 2. *Results of leukocyte in MetS patients and healthy controls.*

Study	MetS			Healthy controls		
	Sample size	Mean	Standard deviation	Sample size	Mean	Standard deviation
Chan-Hee Jung 2013	97	6.29	1.33	1035	5.78	1.37
Eyup Buyukkaya 2014	70	7.23	1.41	71	6.52	0.98
Haixia Liu 2014	4652	6.30	2.00	8480	5.60	1.50
Ali Maleki 2014	344	6.35	1.64	456	6.09	1.89
Chun Pei 2015 (male)	1246	6.48	1.42	3820	6.01	1.44

Study	MetS			Healthy controls		
	Sample size	Mean	Standard deviation	Sample size	Mean	Standard deviation
Chun Pei 2015 (female)	1577	6.10	1.40	3820	5.61	1.38
Chulwoo Rhee 2015	90	6.29	1.21	821	5.72	1.27
Mehmet Kadri Akboga 2015	539	7.41	1.60	607	7.58	1.60
Jamal Ahmadzadeh 2017	3203	7.17	1.72	7911	6.76	1.67
Ali Ugur Uslu 2017	147	7.96	2.63	134	6.69	1.58
Xue-Jiao Yang 2020	919	5.74	1.35	3660	5.32	1.42
Tong Chen 2020 (male)	140	7.24	1.66	343	6.87	1.59
Tong Chen 2020 (female)	277	6.69	1.67	641	6.10	1.53

3.6. Sensitivity Analysis

Sensitivity analysis indicated that the overall pooled SMDs were not affected by a single study (Figure 4).

3.7. Publication Bias

Publication bias was assessed by performing funnel plot (Figure 5). No significant publication bias was found in the analyses (Egger's test P = 0.676; Begg's test P = 0.300).

4. Discussion

MetS is a proinflammatory and prothrombotic state [2, 23]. Insulin resistance and obesity as the main components of MetS, play key roles in its pathophysiology [23-25]. Insulin resistance may lead to metabolic dysregulation, resulting in higher level of inflammatory markers such as total leukocyte and other factors [26-28]. Studies indicate that increased adiposity leads to insulin resistance and macrophage accumulation in the subcutaneous adipose tissue of MetS patients. [28, 29] Adipose tissue dysfunction is integral to the development of obesity-induced inflammation [30], with elevated cytokines and chemokines and dysregulation of adipokines such as TNF-α, SSA, CRP, which could lead to elevated leukocyte level [30-32].

Leukocyte is an objective marker of acute infection, tissue damage, and other inflammatory conditions, and has been testified to play an important role in atherogenesis and thrombus formation [33]. Moreover, as a part of routine complete blood count, leukocyte is a widely conducted and easily affordable biomarker presented by highly standardized analyzing machine in all types of medical organizations, showing its marvelous potency for disease prediction.

The aim of this study is to explore the relationship between leukocyte components and metabolic syndrome. However, due to the limited availability of specific numerical data such as neutrophil, lymphocyte, monocyte and NLR in the screened literature, they were not included in this systematic review and meta-analysis. Therefore, the present study only focused on the association between leukocyte and MetS. We included 11 studies in the meta-analysis. This meta-analysis compared subjects with and without MetS and observed that patients with MetS had significantly higher leukocyte level than those without MetS. Thus, leukocyte was considered a positive predictor. The gender-related results were further confirmed by subgroup analysis, showing that leukocyte level was higher in male patients than female patients. This may be due to the fact that a larger proportion of men have unhealthy lifestyle habits compared to women, such as smoking, drinking alcohol, lack of exercise, etc. All of these can lead to the body being in a chronic low-grade inflammatory state. Subgroup analysis also indicated that leukocyte level was higher in MetS patients than controls in China, Iran and Korea, but no significant difference was detected in turkey studies. This result suggested that country differences may contribute to the heterogeneity of the outcomes, and the possible reasons included differences in diet, lifestyle and gene. Different dietary habits in different countries can lead to changes in the gut microbiota, and these changes can result in different baseline inflammatory states among different ethnicities [23]. Additionally, the level of leukocyte was remarkably higher in MetS patients diagnosed by NCEP ATP III, but results of patients diagnosed by IDF and the Joint statement 2009 showed no significant differences. In this study, the number of included literature was limited, with the majority using NCEP ATP III as the diagnostic criteria. Therefore, the differences are only significant under these particular diagnostic criteria. Since there are not many differences among the three diagnostic criteria mentioned above, statistical significance can only be achieved when an adequate number of literatures is included. More literature is needed to further investigate the differences among the various diagnostic criteria.

Our results on the association between leukocyte count and MetS are consistent with previous studies. According to the study by Chan-Hee Jungs et al. [12], the elevated level of leukocytes was associated with future risk of developing MS in healthy Koreans. Ali Maleki et al [15]. reported that the MetS and non-MetS groups were significantly different in leukocytes. Chun Pei et al [16]. pointed out that a higher level of leukocytes, as an independent risk factor, was associated with a higher risk of developing MetS in the future. These findings demonstrated that leukocyte may be a potentially useful clinical marker for predicting the possibility of developing MetS in healthy populations.

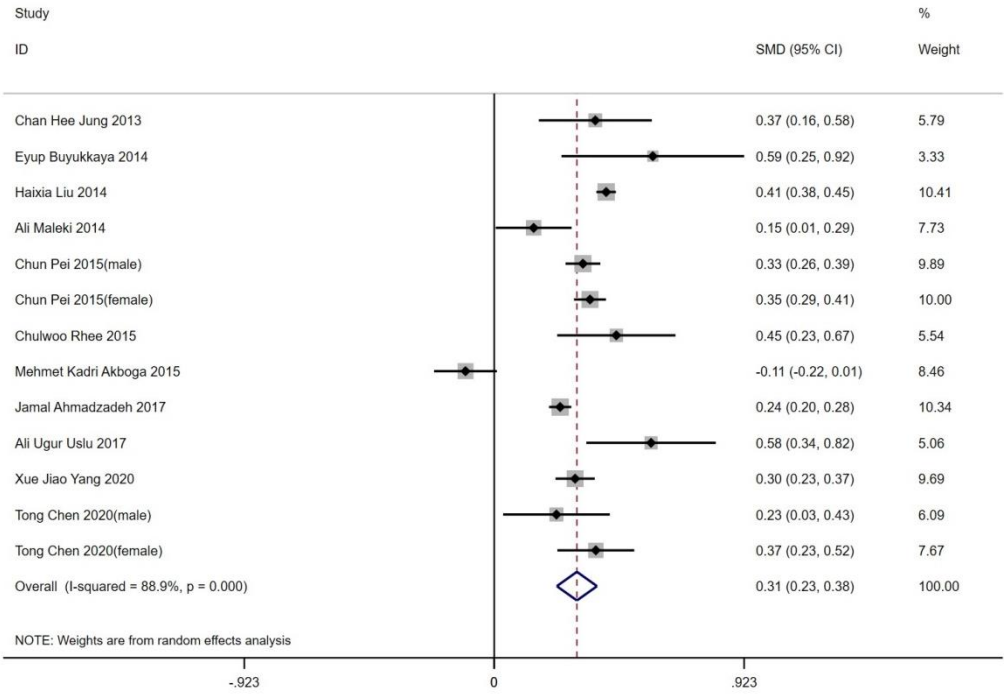
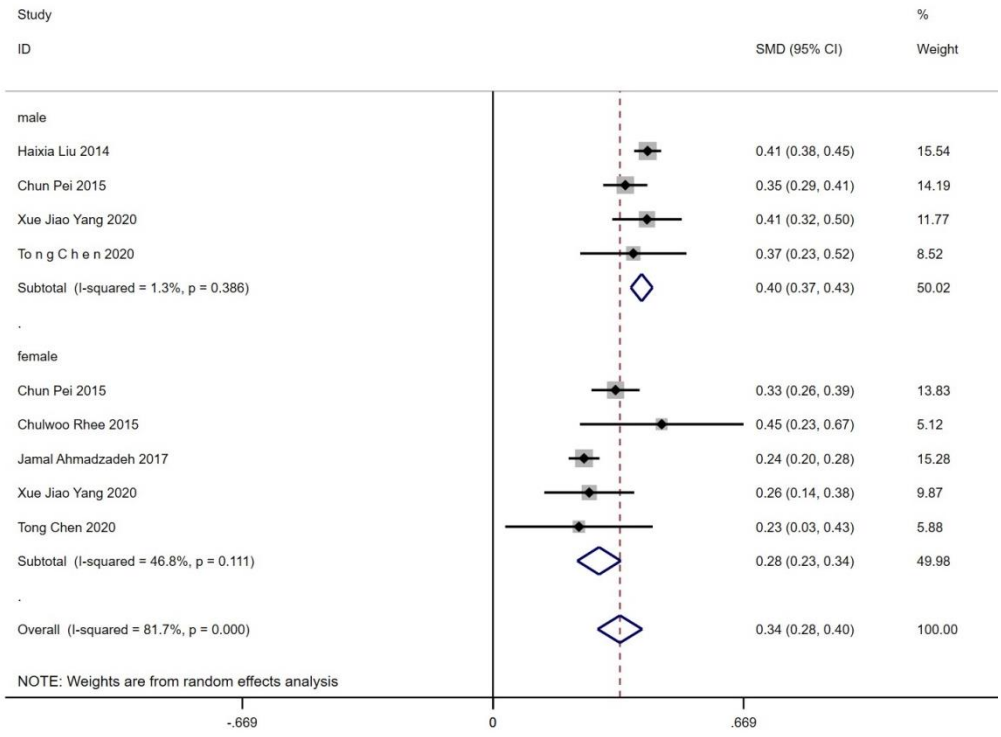
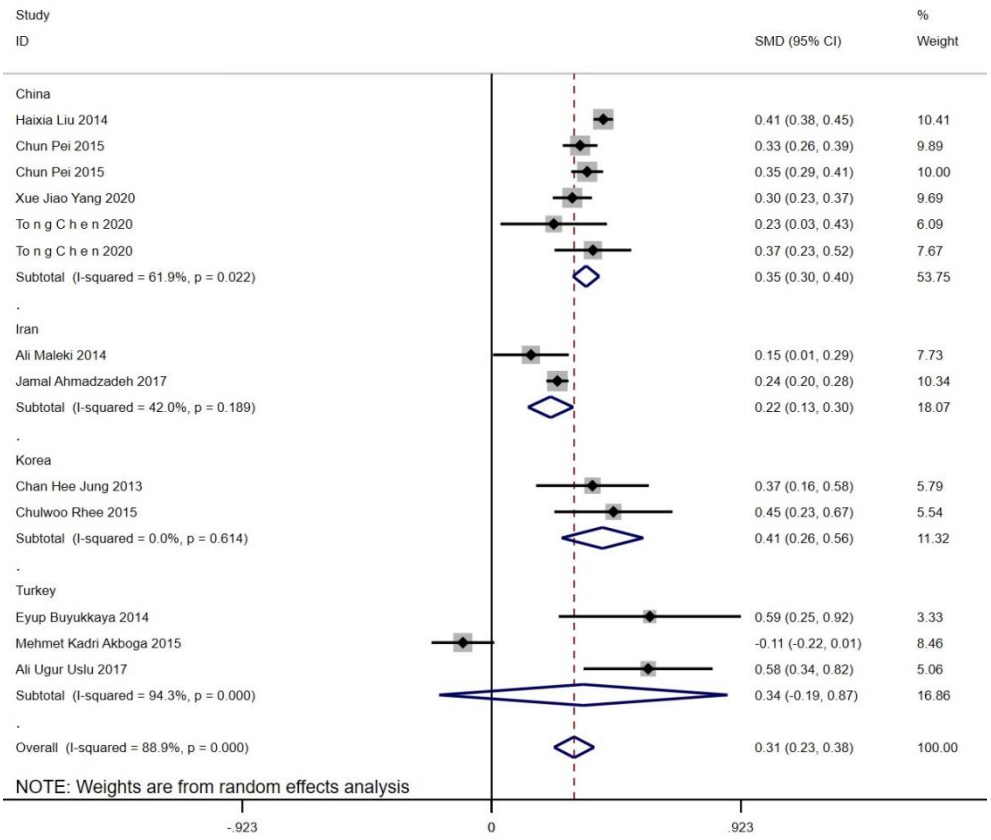


Figure 2. *Forest plot for the comparison of leukocyte level between MetS patients and healthy controls. SMD= standardized mean differences, CI = confidence interval.*



A



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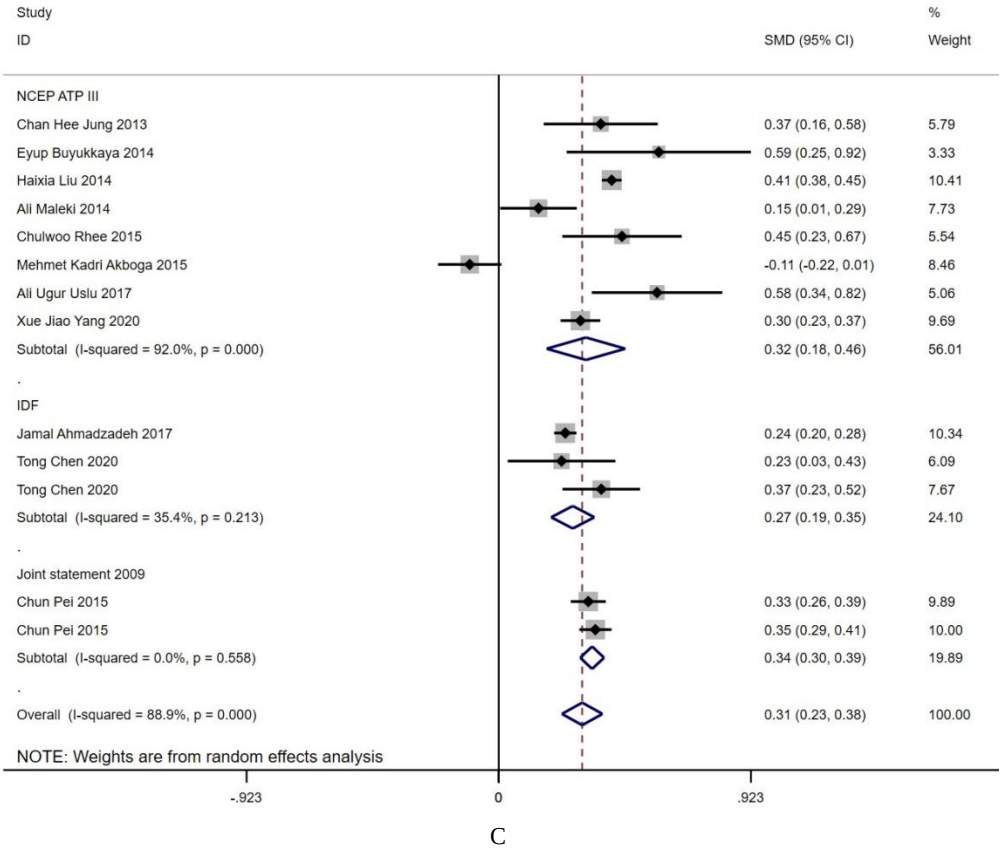

C

Figure 3. *Subgroup analysis for the differences in leukocyte level between metabolic syndrome patients and healthy controls. A, Subgroup analysis based on the gender; B, Subgroup analysis based on the country; C, Subgroup analysis based on the diagnostic criteria.*

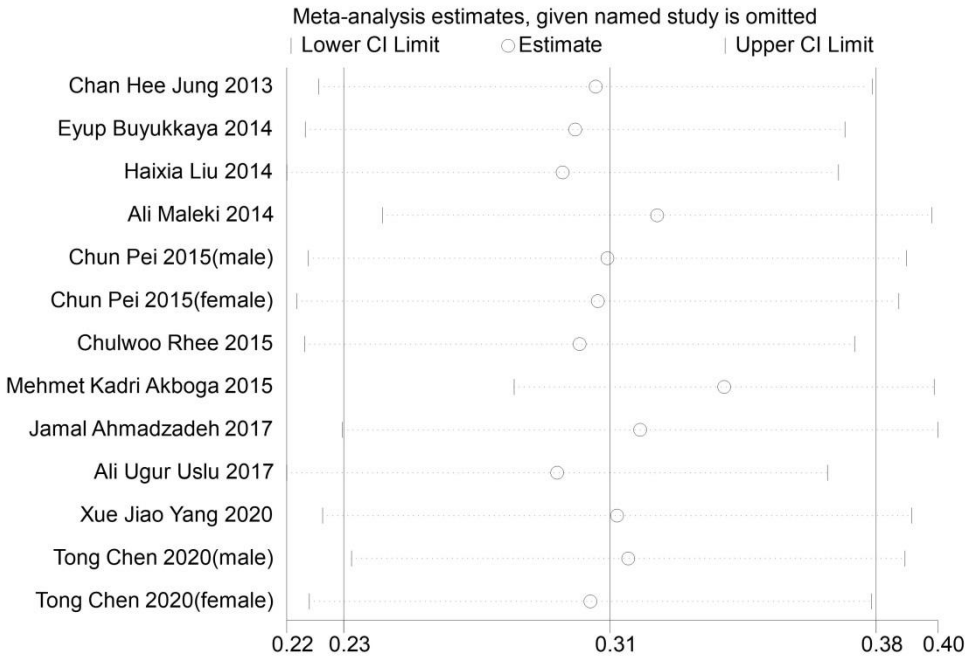

Figure 4. *Sensitivity analysis for assessing the impact of every study on the overall pooled estimate. CI = confidence interval.*

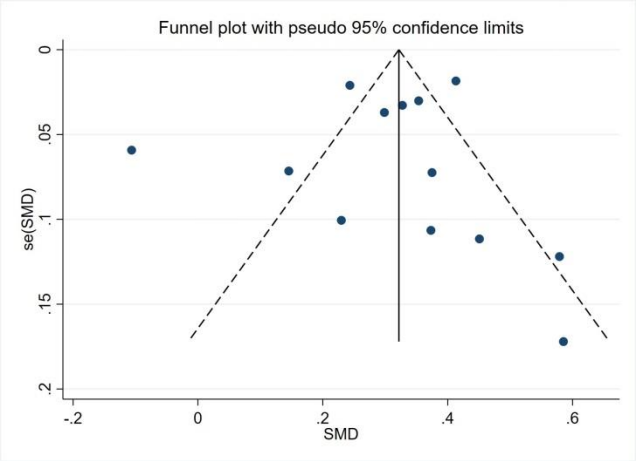

Figure 5. *Sensitivity analysis for assessing the impact of every study on the overall pooled estimate. CI = confidence interval.*

Several limitations of the current study should be mentioned. Firstly, its retrospective nature made it more susceptible to bias. Secondly, it was restricted to studies published in English, which may result in limited inclusion. In addition, heterogeneity is a potential problem that may affect the interpretation of the results of all meta-analyses. Finally, the number of studies on neutrophils, lymphocytes, monocytes and NLR was limited.

5. Conclusions

In conclusion, (1) this study demonstrated that the elevated leukocyte level is associated with the development of MetS, (2) the elevated leukocyte level can provide valuable predictive significance for MetS.

Abbreviations

MetS: Metabolic Syndrome
NLR: Neutrophil to Lymphocyte Ratio
WC: Waist Circumference
HDL: High-Density Lipoprotein
TG: Triglyceride
FPG: Fasting Blood Glucose
NA: Not Accessed
SMD: Standardized Mean Differences
CI: Confidence Interval

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Conflicts of Interest

The authors declare no conflicts of interest.

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