Metabolic syndrome and its components among rheumatoid arthritis patients: A comprehensive updated systematic review and meta-analysis

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Abstract

Background

Estimating the current global prevalence of metabolic syndrome (MetS), and its components, among rheumatoid arthritis (RA) patients is necessary in order to formulate preventative strategies and to ensure there are adequate community resources available for these patients. Furthermore, the association between RA and MetS is controversial and has not previously been comprehensively assessed. Therefore, the present study aimed to: 1) determine the prevalence of MetS, and its components, among RA patients across the world 2) update the odds ratio of MetS in RA patients, compared to healthy controls, using a comprehensive systematic review and meta-analysis.

Methods

International databases, including: the Web of Science, PubMed, Scopus, Embase, CINAHL and other relevant databases were searched to identify English language articles which reported the prevalence and risk of MetS in RA patients between January 2000 and August 2016. The meta-analysis only included studies which clearly described the time and location of the study, utilised adequate sampling strategies, and appropriate statistical analyses.
Results
The meta-analyses of prevalence (70 studies [n = 12612]) and risk (43 studies [n = 35220]) of MetS in RA patients were undertaken separately. The overall pooled prevalence of MetS was 30.65% (95% CI: 27.87–33.43), but this varied from 14.32% (95% CI: 10.59–18.05) to 37.83% (95% CI: 31.05–44.61), based upon the diagnostic criteria used. The prevalence of MetS also varied slightly between males (31.94%, 95% CI: 24.37–39.51) and females (33.03%, 95% CI: 28.09–37.97), but this was not statistically significant. The overall pooled odds ratio (OR) of MetS in RA patients, compared to healthy controls, was 1.44 (95% CI: 1.20–1.74), but this ranged from 0.70 (95% CI: 0.27–1.76) to 4.09 (95% CI: 2.03–8.25), depending on the criteria used. The mean age and diagnostic criteria of MetS were identified as sources of heterogeneity in the estimated odds ratios between studies (P<0.05).

Conclusions
According to the high prevalence of MetS in RA patients, and high risk of MetS, measuring metabolic syndrome in RA patients is strongly recommended. Furthermore, as high waist circumference (WC) is the most common metabolic syndrome component, more attention must be paid to nutrition and weight loss among those with RA.

Introduction
Metabolic syndrome (MetS) is comprised of a group of risk factors for type 2 diabetes and cardiovascular diseases, including insulin resistance, abdominal obesity, dyslipidemia, blood pressure, and impaired fasting glucose[1]. The most common clinical manifestations of MetS include: abdominal obesity, hypertriglyceridaemia, reduced high-density lipoprotein cholesterol (HDL-C), hyperglycaemia, and high blood pressure (BP)[2]. MetS is responsible for a three-fold increase in the risk of atherosclerotic cardiovascular diseases (CVDs) and increased mortality from CVD, as well as all-causes, compared to the general population [3]. MetS is also associated with a fourfold increased relative risk of developing diabetes [4, 5]. There are eight commonly used definitions for MetS, but the National Cholesterol Education Programme-Adult Treatment Panel III (NCEP ATP III) and the International Diabetes Federation (IDF) definitions are the most commonly used [6]. These definitions have many similarities, but they differ on several components and on the cut-off points used (Table 1).

Therefore, although we could expect slight differences in prevalence rates, according to the criteria used in each study, genetic and geographical differences may also contribute to differences in the rates of MetS. For example, using the ATP III definition, Ford et al. reported the prevalence rate of metabolic syndrome in the USA to be 34.3% [3], while Tillin et al. reported the age-adjusted rates were 18.4% for men and 14.4% for women among Europeans, 28.8% for men and 31.8% for women in South Asians, and 15.5% for men and 23.4% for women in African-Caribbeans. Further, the prevalence rate was reported to be 15.7% in Taiwan, using the same criteria[7, 8].

Rheumatoid arthritis (RA) is a chronic inflammatory disorder of unknown etiology [9] that has a prevalence rate of approximately 0.5 to 1% [10]. Rheumatoid arthritis and metabolic syndrome are considered to be diseases with common traits that can increase the risk of cardiovascular disease[11], with previous research showing an association between the two[12]. Higher frequencies of insulin resistance and MetS have been reported in patients with RA [12, 13], with the frequency of MetS in RA patients ranging from 14 to 56% [14]. This variation can
Table 1. Summary of the MetS definitions.

| Definitions                                      | WHO                              | NCEP-ATP III                     | IDF                              | EGIR                             | AACE                             | AHA/NHLBI                         | ATP III                           | JS 2009                          |
|--------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|
| Number of Criteria                               | Two or more of:                 | Three or more of:                | Two or more of:                  | Two or more of:                  | Obesity and two or more of:      | Three or more of:                 | Three or more of:                 | Three or more of:                 |
| Obesity                                          | BMI > 30 and/or WHR > 0.9 (men), |                                  |                                  |                                  |                                  |                                   |                                   |                                  |
|                                                  | WHR > 0.85 (women)              |                                  |                                  |                                  |                                  |                                   |                                   |                                  |
|                                                  | WC ≥ 102 cm (men), WC ≥ 88 cm   | WC ≥ 94 cm (men), WC ≥ 80 cm (women) | WC ≥ 94 cm (men), WC ≥ 80 cm (women) | WC ≥ 102 cm (men), WC ≥ 88 cm (women) | BMI ≥ 30 kg/m2                  |                                   |                                   | Population- and country-specific definitions |
| Blood pressure mmHg                              | ≥ 140/90                        | ≥ 130/85 or treatment            | ≥ 130/85 or treatment            | ≥ 140/90                        | ≥ 130/85 or treatment            | ≥ 130/85 or treatment            | ≥ 130/85 or treatment            |                                  |
| Dyslipidemia:                                    |                                  |                                  |                                  |                                  |                                  |                                   |                                   |                                  |
| HDL-C                                           | ≥ 35 mg/dL (0.9 mmol/L) in men   | ≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/dL (1.29 mmol/L) in men, or treatment | ≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/dL (1.29 mmol/L) in women, or treatment | ≥ 39 mg/dL (1.0 mmol/L) or treatment | ≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/dL (1.29 mmol/L) in women, or treatment | ≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/dL (1.29 mmol/L) in women, or treatment | ≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/dL (1.29 mmol/L) in women, or treatment |                                  |
| Triglycerides                                    | ≥178 mg/dL (2.0 mmol/L) or treatment | ≥150 mg/dL (1.7 mmol/L) or treatment | ≥150 mg/dL (1.7 mmol/L) or treatment | ≥150 mg/dL (1.7 mmol/L) or treatment | ≥150 mg/dL (1.7 mmol/L) or treatment | ≥150 mg/dL (1.7 mmol/L) or treatment | ≥150 mg/dL (1.7 mmol/L) or treatment |                                  |
| Glucose Intolerance or Fasting Plasma Glucose    | ≥110 mg/dL (5.6 mmol/L) or T2D  | ≥100 mg/dL (5.6 mmol/L) or T2D   | ≥100 mg/dL (5.6 mmol/L) or T2D   | ≥110 mg/dL (6.1 mmol/L) or T2D   | ≥110 mg/dL (6.1 mmol/L) or T2D   | ≥100 mg/dL (5.6 mmol/L) or T2D   | ≥110 mg/dL (6.1 mmol/L) or T2D   |                                  |

BMI = body mass index; JC = Joint Consensus; DM = diabetes mellitus; EGIR = European Group against Insulin Resistance; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation; IGT = impaired glucose tolerance; IR = insulin resistance; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel; AACE = American Association of Clinical Endocrinologists; AHA/NHLBI = The American Heart Association / National Heart, Lung, and Blood Institute; JS = Joint Statement; T2 D, type II diabetes mellitus; WC = waist circumference; WHO = World Health Organization; WHR = waist hip ratio.

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be explained by differences in the definition of MetS, along with differences in ethnicity, geographic area, study design, and study population. However, although many studies have reported a higher prevalence of MetS among RA patients, compared to the general population [15, 16], a number of studies have reported a higher prevalence of MetS in the healthy controls [2].

Research measuring the prevalence of MetS in RA patients has resulted in a wide range of estimates across the world. In addition, research measuring the prevalence of metabolic syndrome using a large sample size is rare. Furthermore, there have been very few meta-analyses on the prevalence of MetS in patients with rheumatoid arthritis [11]. Therefore, the present study aimed to: 1) determine the prevalence of MetS, and its components, in RA patients across the world 2) update the odds ratio of MetS in RA patients, compared to healthy controls, using a comprehensive systematic review and meta-analysis.

Methods

Search strategy and study selection

The current systematic review and meta-analysis was conducted according to PRISMA guidelines [17]. A systematic review was undertaken of English-language medical literature
published between January 2000 and August 2016 to identify scientific papers reporting the prevalence and risk of metabolic syndrome and its components (i.e., waist circumference—WC, blood pressure—BP, high-density lipoprotein cholesterol—HDL-C, Triglycerides—TG, fasting blood sugar—FBS) among rheumatoid arthritis patients.

International databases, including: the Web of Science, Medline, Scopus, Embase, CABI, CINAHL, DOAJ, Index Medicus for Eastern Mediterranean Region-IMEMR and Google Scholar were searched using the following medical subject headings (MeSH): "Metabolic Syndrome", "Dysmetabolic Syndrome", "Cardiovascular Syndrome", and "Insulin Resistance Syndrome", combined with "Rheumatoid Arthritis", "Prevalence", "Odds Ratio", "Comparative Cross-sectional Studies" and "case-control studies". The search strategy for Medline was developed first and then adapted for the remaining databases. More detailed information regarding the search strategy is presented in Box 1. The grey literature were searched using Google Scholar, as recommended [18], using the abovementioned search strategy. An expert in this field was also consulted to identify additional papers.

All publications were categorized using Endnote X6. The title and abstract of identified publications were systematically screened and full texts were obtained for those which passed the initial screening. All full text publications were then independently evaluated by two reviewers (SS and JH) for inclusion in the review. Disagreements between the reviewers were resolved by consensus using a third expert (MN). In this study, blinding and task separation were also applied to study selection.

**Box 1. Search strategy for MEDLINE (MeSH, Medical Subject Headings).**

1: Metabolic Syndrome [Text Word] OR Metabolic Syndrome [MeSH Terms]
2: Dysmetabolic Syndrome [Text Word] OR Dysmetabolic Syndrome [MeSH Terms]
3: Cardiovascular Syndrome [Text Word] OR Cardiovascular Syndrome [MeSH Terms]
4: Insulin Resistance Syndrome [Text Word] OR Insulin Resistance Syndrome [MeSH Terms]
5: 1 OR 2 OR 3 OR 4
6: Rheumatoid Arthritis [Text Word] OR Rheumatoid Arthritis [MeSH Terms]
7: 5 AND 6
8: Prevalence [Text Word] OR Prevalence [MeSH Terms]
9: Odds Ratio [Text Word] OR Odds Ratio [MeSH Terms]
10: Risk Ratio [Text Word] OR Risk Ratio [MeSH Terms]
11: Cross-Product Ratio [Text Word] OR Cross-Product Ratio [MeSH Terms]
12: 8 OR 9 OR 10 OR 11
13: Cross-sectional Studies [Text Word] OR Cross-sectional Studies [MeSH Terms]
14: Case-Control Studies [Text Word] OR Case-Control Studies [MeSH Terms]
15: Comparative cross-sectional Studies [Text Word] OR Comparative cross-sectional Studies [MeSH Terms]
16: 13 OR 14 OR 15
17: 7 AND 12 AND 16
All English language observational (cross-sectional and comparative cross-sectional) studies on the prevalence of metabolic syndrome were included in the current study if they clearly described the date of data collection and study location, used appropriate sampling strategies, and conducted appropriate statistical analyses. Case studies and letters to the editor were excluded, along with systematic reviews or meta-analyses. Lastly, studies undertaken on patients with other disorders were also excluded.

Data extraction and quality assessment

Study characteristics (first author’s name, date of publication, and country of origin), participant characteristics (gender, age, and sample size), and MetS prevalence (based on the different criteria) were extracted using the full text reviews. The quality of each included study was also assessed using the STROBE checklist [19].

Statistical analysis

All statistical analyses were undertaken using Review Manager (RevMan) Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The prevalence of metabolic syndrome, and its five components, among rheumatoid arthritis patients were pooled using a random-effects model and presented in a forest plot. The odds ratios for metabolic syndrome in rheumatoid arthritis patients, based upon the different diagnostic criteria, in comparative cross-sectional studies were also pooled using a random-effects model and presented in a forest plot. Statistical heterogeneity was assessed using the I^2 index and a random-effects model was used when the I^2 index was > 0.6. Stata software version 13 (Stata Corp, College Station, TX, USA) was used to determine which factors were responsible for any observed heterogeneity using meta-regression. Publication bias, with regards to the ORs between MetS and RA was assessed using a Funnel plot and Begg’s correlation test [20].

Results

After removing duplicates, our primary search found 237 relevant articles. Following the exclusion of all non-eligible studies a total of 70 cross-sectional studies and 43 comparative cross-sectional studies, from 25 countries, were retained to estimate the prevalence and risk of metabolic syndrome among RA patients. The details of our study selection method are shown in Fig 1. The majority of the studies reporting MetS prevalence (55 studies) included both male and female patients who were aged > 18 years. The lowest and highest prevalence of MetS in rheumatoid arthritis patients reported were 10.6% and 55.5%, respectively. More detailed information about each included studies can be found in Table 2.

The estimated pooled prevalence, with 95% confidence interval (the diamond below the graph shows the pooled prevalence and the horizontal lines define the reported 95% confidence interval in each study) are presented in graphs by gender and by MetS definition.

Total MetS prevalence in RA patients by gender

Using a random effects model, the estimated worldwide prevalence rate of MetS among RA patients was 30.65% (95% CI: 27.87–33.43) (Fig 2). In addition, information on the prevalence of MetS by gender was available from 19 studies for males and 30 for females. The prevalence rates among males was 31.94% (95% CI: 24.37–39.51) and for females this was 33.03% (95% CI: 28.09–37.97) (Figs 3 and 4).
MetS prevalence in RA patients by criteria/definition

The pooled MetS prevalence rates for the eight definitions are: WHO—19.96% (95% CI: 17.12–22.81), NCEP/ATP III—31.55% (95% CI: 27.95–35.15), IDF—32.84% (95% CI: 24.98–40.71), EGIR—14.32% (95% CI: 10.59–18.05), ACCE—24.6% (95% CI: 19.29–30.91), AHA/NHLBI—31.39% (95% CI: 20.61–42.17), ATP III—37.83% (95% CI: 31.05–44.61) and JS 2009—27.54% (95% CI: 17.85–37.24) (Fig 5).
Table 2. Worldwide prevalence (95% CI) of metabolic syndrome in rheumatoid arthritis patients.

| First Author | Country     | Criteria          | DOP       | Age Range | Mean Age | Gender | N. of RA Patients | Prevalence of MetS in RA Patients (%) | Reference |
|--------------|-------------|-------------------|-----------|-----------|----------|--------|-------------------|--------------------------------------|-----------|
|              | Total       | Male              | Female    | Total     | Male     | Female |                  |                                      |           |
| Lee SH       | Korea       | AHA/NHLBI         | 2016      | ≥12       | 63.6     | Both   | 598               | 36.4 34.5 36.9                         | [37]      |
| Hugo M       | France      | IDF               | 2016      | 18–75     | 57.6     | Both   | 575               | 24.0 25.0 24.0                         | [38]      |
| Zafar ZA     | Pakistan    | NCEP-ATP III      | 2016      | 20–60     | 43.8     | Both   | 384               | 31.3 18.5 35.5                         | [35]      |
| Oliveira BMGB| Brazil      | NCEP-ATP III      | 2016      | 55.5      | Female   | 107    | 51.4              | 51.4                                  | [24]      |
| Oliveira BMGB| Brazil      | IDF               | 2016      | 55.5      | Female   | 107    | 53.4              | 53.4                                  | [24]      |
| Muller R     | Estonia     | NCEP-ATP III      | 2016      | >12       | 41.5     | Both   | 72               | 16.7 66 35                           | [33]      |
| Dihingia P   | India       | NCEP-ATP III      | 2015      | 52–68     | 59       | Both   | 583               | 43.1 40.0 43.7                         | [41]      |
| Tanayakom P  | Thailand    | NCEP-ATP III      | 2015      | 59        | Both     | 267    | 16.1 12.9 16.5     |                                      | [42]      |
| Parra-Salcedo F | Mexico | AHA/NHLBI         | 2015      | -         | 38.1     | Both   | 160               | 28.0                                  | [43]      |
| Parra-Salcedo F | Mexico | IDF               | 2015      | -         | 38.1     | Both   | 160               | 18.0                                  | [43]      |
| Parra-Salcedo F | Mexico | NCEP-ATP III     | 2015      | -         | 38.1     | Both   | 160               | 24.0                                  | [43]      |
| Craciun L    | Romania     | IDF-AHA           | 2014      | 32–79     | 55.2     | Both   | 51               | 9.0 10.52 82.47                       | [23]      |
| Craciun L    | Romania     | NCEP-ATP III      | 2014      | 32–79     | 55.2     | Both   | 51               | 23.0                                  | [23]      |
| Craciun L    | Romania     | IDF               | 2014      | 32–79     | 55.2     | Both   | 51               | 18.0                                  | [23]      |
| Craciun L    | Romania     | AHA               | 2014      | 32–79     | 55.2     | Both   | 51               | 14.0                                  | [23]      |
| Bilecik NA   | Turkey      | IDF               | 2014      | 24–65     | 52.0     | Female | 100              | 33.0                                  | [44]      |
| Bilecik NA   | Turkey      | NCEP-ATP III      | 2014      | 24–65     | 52.0     | Female | 100              | 27.0 27.0                             | [44]      |
| Özmên M      | Turkey      | NCEP-ATP III      | 2014      | -         | 51.0     | Both   | 52               | 17.30                                 | [45]      |
| Özmên M      | Turkey      | WHO               | 2014      | -         | 51.0     | Both   | 52               | 28.80                                 | [45]      |
| Kumar BS     | India       | IDF               | 2014      | >18       | 46.0     | Both   | 54               | 29.0                                  | [46]      |
| Kumar BS     | India       | NCEP-ATP III      | 2014      | >18       | 46.0     | Both   | 54               | 31.0                                  | [46]      |
| Abourazzak FE| Morocco     | IDF               | 2014      | >16       | 49.0     | Both   | 179              | 30.7                                  | [26]      |
| Abourazzak FE| Morocco     | NCEP-ATP III      | 2014      | >16       | 49.0     | Both   | 179              | 29.0                                  | [26]      |
| Abourazzak FE| Morocco     | AACE 2003         | 2014      | >16       | 49.0     | Both   | 179              | 24.6                                  | [26]      |
| Salinas MJH  | Argentina   | ATP III           | 2013      | -         | 55.5     | Both   | 409              | 30.0 62.0 23.8                        | [47]      |
| Salinas MJH  | Argentina   | IDF               | 2013      | -         | 55.5     | Both   | 409              | 35.0                                  | [47]      |
| Abdul-Qahar  | Iraq        | NCEP-ATP III      | 2013      | -         | 46.9     | Both   | 203              | 51.2 12.0 92.0                        | [48]      |
| Rostam S     | Morocco     | NCEP-ATP III-2004 | 2013      | -         | 49.0     | Both   | 120              | 30.8 10.0 32.7                       | [49]      |
| Rostam S     | Morocco     | NCEP-ATP III-2001 | 2013      | -         | 49.0     | Both   | 120              | 24.6                                  | [49]      |
| Rostam S     | Morocco     | WHO               | 2013      | -         | 49.0     | Both   | 120              | 20.0                                  | [49]      |
| Rostam S     | Morocco     | IDF               | 2013      | -         | 49.0     | Both   | 120              | 48.6                                  | [49]      |
| Rostam S     | Morocco     | EGIR              | 2013      | -         | 49.0     | Both   | 120              | 18.0                                  | [49]      |
| Rostam S     | Morocco     | JC 2009           | 2013      | -         | 49.0     | Both   | 120              | 32.3                                  | [49]      |
| Lee SG       | Korea       | NCEP-ATP III      | 2013      | 22–76     | 50.6     | Female | 84               | 19.0                                  | [34]      |
| Ormseth MJ   | USA         | ATP III           | 2013      | >18       | 54.0     | Both   | 162              | 36.0                                  | [50]      |
| Karakoc      | Turkey      | IDF               | 2012      | -         | 49.8     | Both   | 54               | 42.6                                  | [51]      |
| Manka V      | Slovakia    | IDF               | 2012      | >18       | 58.8     | Both   | 87               | 48.3                                  | [52]      |
| Manka V      | Slovakia    | NCEP-ATP III      | 2012      | >18       | 58.8     | Both   | 87               | 44.8                                  | [52]      |
| Manka V      | Slovakia    | AHA/NHLBI         | 2012      | >18       | 58.8     | Both   | 87               | 47.1                                  | [52]      |
| Cunha VR Da  | Brazil      | NCEP-ATP III      | 2012      | >18       | 56.8     | Both   | 283              | 39.2                                  | [53]      |
| Goshayeshi L | Iran        | NCEP-ATP III      | 2012      | -         | 45.5     | Both   | 120              | 45.2                                  | [21]      |
| Bkaer JF     | USA         | IDF               | 2012      | 18–85     | 49.5     | Both   | 499              | 10.6                                  | [54]      |

(Continued)
MetS prevalence in rheumatoid arthritis patients by MetS component

The MetS components of FBS, HDL-C, BP, Triglyceride and Waist Circumstance (WC) were reported by 26, 22, 19 and 24 studies, respectively. The pooled MetS prevalence rates, by component, were: FBS—19.47% (95% CI: 15.69–23.25), HDL—41.78% (95% CI: 28.73–54.84), BP—48.65% (95% CI: 41.03–56.26), Triglyceride—28.43% (95% CI: 22.3–34.57) and WC—52.63% (95% CI: 43.76–61.5) (S 1–5 Appendix).

Risk of MetS in rheumatoid arthritis patients by criteria/definition

In this section the prevalence of MetS in RA patients and among healthy controls were compared (Table 3). The pooled estimates identified a significant positive association between rheumatoid arthritis and the risk of MetS (OR = 1.44; 95% CI: 1.20–1.74). The odds ratios for

Table 2. (Continued)

| First Author   | Country | Criteria | DOP Age Range | Mean Age | Gender | N. of RA Patients | Prevalence of MetS in RA Patients (%) | Reference |
|----------------|---------|----------|---------------|----------|--------|-------------------|--------------------------------------|-----------|
| Crowson CS     | USA     | NCEP-ATP III 2011 | 18–58.8 | Both    | 232 58 174 | 33.0 36.0 32.0 | [31]                                  |
| Sahaberi M     | Iran    | IDF 2011 | - 45.5 | Both    | 120 14 106 | 30.8 28.6 41.5 | [55]                                  |
| Sahaberi M     | Iran    | NCEP-ATP III 2011 | - 45.5 | Both    | 120 14 106 | 45.2 28.6 37.7 | [55]                                  |
| Karimi M       | Iran    | NCEP 2011 | 18–48.3 | Female  | 92 - 92 | 27.2 - 27.2 | [22]                                  |
| Karimi M       | Iran    | WHO 2011 | - 48.3 | Female  | 92 - 92 | 19.6 - 19.6 | [22]                                  |
| Mok CC         | Hong Kong | JS 2009 | 18–53.3 | Both    | 699 133 566 | 20.0 | [56]                                  |
| Dao HH         | Vietnam | IDF 2010 | 26–73 | Female  | 105 - 105 | 40.9 - 40.9 | [57]                                  |
| Dao HH         | Vietnam | NCEP-ATP III 2004 | 26–73 | Female  | 105 - 105 | 32.4 - 32.4 | [57]                                  |
| Dao HH         | Vietnam | NCEP-ATP III 2001 | 26–73 | Female  | 105 - 105 | 24.7 - 24.7 | [57]                                  |
| Dao HH         | Vietnam | JS 2009 | 26–73 | Female  | 105 - 105 | 32.4 - 32.4 | [57]                                  |
| Dao HH         | Vietnam | WHO 2004 | 26–73 | Female  | 105 - 105 | 19.0 - 19.0 | [57]                                  |
| Dao HH         | Vietnam | EGIR 2010 | 26–73 | Female  | 105 - 105 | 16.2 - 16.2 | [57]                                  |
| Raterman H G   | Netherlands | NCEP 2010 | 50–75 | Both    | 236 79 157 | 19.9 | [58]                                  |
| Solomon A      | South Africa | NCEP-ATP III 2001 | - | 27.2 | Both    | 291 32 259 | 31.3 | [59]                                  |
| Solomon B      | South Africa | NCEP-ATP III 2010 | - | 27.2 | Both    | 335 65 270 | 20.3 | [59]                                  |
| Giles J        | USA     | NCEP-ATP III 2010 | 45–84 | Both    | 131 51 80 | 36.0 | [60]                                  |
| Santos MJ      | Portugal | ATP III 2010 | ≥18 | 49.2 | Female  | 98 98 25.5 | [61]                                  |
| Toms TE        | UK      | IDF 2009 | 55.5–69.6 | 63.1 | Both    | 387 105 282 | 45.3 52.7 42.6 | [25] |
| Toms TE        | UK      | NCEP-ATP III 2004 | 55.5–69.6 | 63.1 | Both    | 387 105 282 | 40.1 42.5 39.2 | [25] |
| Toms TE        | UK      | NCEP-ATP III 2001 | 55.5–69.6 | 63.1 | Both    | 387 105 282 | 38.3 40.0 37.7 | [25] |
| Toms TE        | UK      | WHO 2009 | 55.5–69.6 | 63.1 | Both    | 387 105 282 | 19.4 25.5 17.2 | [25] |
| Toms TE        | UK      | EGIR 2009 | 55.5–69.6 | 63.1 | Both    | 387 105 282 | 12.1 22.6 8.2 | [25] |
| Chung CP       | USA     | WHO 2008 | ≥18 | 59 | Both    | 66 18 48 | 42.0 | [29]                                  |
| Zonana-Nachach A | Mexico | NCEP-ATP III 2008 | - | 42.9 | Both    | 107 | 18.7 | [30]                                  |
| Karvounaris SA | Greece  | ATP III 2007 | ≥18 | 63.0 | Both    | 200 53 147 | 44.0 39.6 45.6 | [32] |
| Montagna G La  | Italy   | NCEP-ATP III 2007 | - | 53.8 | Both    | 45 3 42 | 55.5 | [62]                                  |

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Fig 2. Forest plot of MetS prevalence in RA Patients.

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MetS in rheumatoid arthritis patients, according to the definition used, were: **WHO**—OR = 1.45 (95% CI: 0.9–2.33), **NCEP/ATP III**—OR = 1.52 (95% CI: 1.12–2.06), **IDF**—OR = 1.52 (95% CI: 0.84–2.77), **EGIR**—OR = 1.65 (95% CI: 0.95–2.87), **ACCE**—OR = 4.09 (95% CI: 2.03–8.25), **AHA/NHBI**—OR = 0.7 (95% CI: 0.27–1.76), **ATP III**—OR = 1.22 (95% CI: 0.71–2.1), and **JS 2009**—OR = 1.58 (95% CI: 0.84–2.94) (Fig 6).

**Publication bias**

In order to assess publication bias in relation to the OR for MetS and RA, funnel plots and Begg’s correlation were used. These found no evidence of any publication bias (Fig 7).

**Meta-regression**

To assess the sources of heterogeneity, four variables were included in a univariable meta-regression. Our results indicated that the study date (P = 0.60) and country (P = 0.38) were not responsible for the heterogeneity in the ORs for MetS in RA patients, compared to healthy controls, but mean age (P = 0.03) and diagnostic criteria (P = 0.04) could be considered sources of heterogeneity. Hence, subgroup analysis was undertaken based upon the diagnostic criteria.

**Discussion**

The present study found a MetS prevalence of 30.65% among RA patients, but this rate ranged from 14.32% to 37.83%, depending upon the MetS definition used. The relatively high degree
of variability in MetS prevalence, according to the MetS definition used, is clearly a substantial issue that permeates the literature on this topic. For example, research in Asia has reported the prevalence of MetS to be 45.2% among RA patients using the NCEP-ATP III criteria [21] and 19.6% when using the WHO definition [22]. In Europe the prevalence rates reported, according to criteria used were: AHA (27.4%), IDF (35.2%), IDF-AHA (37.2%) and NCEP-ATP III (23.0%) [23]. Furthermore, based on the NCEP-ATP III criteria, Oliveira et al. found that the prevalence of MetS among RA patients in South American was 51.4%, but using the IDF criteria this proportion was 53.4% [24]. Much larger differences have been reported in research from the UK, with MetS prevalence ranging from 8.2% to 42.6% [25], depending upon the definition used. Moreover, in a cross-sectional study which used three definitions (NCEP-ATP

| Study or Subgroup               | Prevalence | SE  | Weight | Prevalence IV, Random, 95% CI | Prevalence IV, Random, 95% CI |
|---------------------------------|------------|-----|--------|------------------------------|------------------------------|
| AbdulQahar NCEP-ATP3 2013       | 56.8       | 3.89| 3.3%   | 56.80 [49.18, 64.42]         |                             |
| Bilecik IDF 2014               | 33.0       | 4.7 | 3.2%   | 33.00 [23.79, 42.21]         |                             |
| Bilecik NCEP ATP3 2014         | 27.0       | 4.44| 3.3%   | 27.00 [18.30, 35.70]         |                             |
| Crowson NCEP ATP3 2011         | 32.0       | 3.54| 3.4%   | 32.00 [25.06, 38.94]         |                             |
| Dao EGIR 2010                  | 16.2       | 3.6 | 3.4%   | 16.20 [9.14, 23.26]          |                             |
| Dao IDF 2010                   | 40.9       | 4.8 | 3.2%   | 40.90 [31.49, 50.31]         |                             |
| Dao JS 2009 2010               | 32.4       | 4.57| 3.2%   | 32.40 [23.44, 41.36]         |                             |
| Dao NCEP ATP 3 2001 2010       | 24.7       | 4.21| 3.3%   | 24.70 [16.45, 32.95]         |                             |
| Dao NCEP ATP 3 2004 2010       | 32.4       | 4.57| 3.2%   | 32.40 [23.44, 41.36]         |                             |
| Dao WHO 2010                   | 19.0       | 3.83| 3.4%   | 19.00 [11.49, 26.51]         |                             |
| Ghazaly ATP3 2015              | 49.25      | 6.11| 3.0%   | 49.25 [37.27, 61.23]         |                             |
| Hugo IDF 2016                   | 24.0       | 6.59| 2.9%   | 24.00 [11.08, 36.92]         |                             |
| Karvounaris ATP3 2007          | 45.6       | 4.11| 3.3%   | 45.60 [37.54, 53.66]         |                             |
| Lee AHA 2016                   | 36.88      | 2.18| 3.5%   | 36.88 [32.61, 41.15]         |                             |
| Lee NCEP ATP3 2013             | 19.4       | 4.28| 3.3%   | 19.00 [10.61, 27.39]         |                             |
| Oliviera IDF 2016              | 53.4       | 4.82| 3.2%   | 53.40 [43.95, 62.85]         |                             |
| Oliviera NCEP-ATP3 2016        | 51.4       | 4.83| 3.2%   | 51.40 [41.93, 60.87]         |                             |
| Rostam NCEPATP3 2004 2013      | 32.72      | 4.47| 3.3%   | 32.72 [23.96, 41.48]         |                             |
| Sahebbari IDF 2011             | 41.5       | 4.79| 3.2%   | 41.50 [32.11, 50.89]         |                             |
| Sahebbari NCEP ATP3 2011       | 37.7       | 4.71| 3.2%   | 37.70 [28.47, 46.93]         |                             |
| Salamon ATP3 2015              | 43.7       | 2.26| 3.5%   | 43.70 [39.27, 48.13]         |                             |
| Salinas ATP3 2013              | 23.8       | 2.31| 3.5%   | 23.80 [19.27, 28.33]         |                             |
| Santos ATP3 2010               | 25.5       | 4.4 | 3.3%   | 25.50 [16.88, 34.12]         |                             |
| Tanayakom NCEP-ATP3 2015       | 16.52      | 2.42| 3.5%   | 16.52 [11.78, 21.26]         |                             |
| Toms EGIR 2004                 | 8.2        | 1.63| 3.6%   | 8.20 [5.01, 11.39]           |                             |
| Toms IDF 2004                  | 42.6       | 2.94| 3.5%   | 42.60 [36.84, 48.36]         |                             |
| Toms NCEP ATP 3 2001 2004      | 37.7       | 2.89| 3.5%   | 37.70 [32.04, 43.36]         |                             |
| Toms NCEP ATP 3 2004 2004      | 39.2       | 2.91| 3.5%   | 39.20 [33.50, 44.90]         |                             |
| Toms WHO 2004                  | 17.2       | 2.25| 3.5%   | 17.20 [12.79, 21.61]         |                             |
| Zafar NCEP-ATP3-2016           | 35.5       | 2.82| 3.5%   | 35.50 [29.97, 41.03]         |                             |

Total (95% CI) 100.0% 33.03 [28.09, 37.97]

Heterogeneity: Tau² = 174.57; Chi² = 497.69, df = 29 (P < 0.00001); I² = 94%
Test for overall effect: Z = 13.11 (P < 0.00001)
Fig 5. Forest plot of MetS prevalence among RA Patients by definition/criteria.

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### Table 3. Worldwide prevalence (95% CI) of metabolic syndrome in rheumatoid arthritis patients compared to healthy controls.

| First Author | Country | Criteria | DOP | Gender | N. RA Patients | Total MetS Prev. (%) | N. Healthy Controls | Total MetS Prev. (%) | Reference |
|--------------|---------|----------|-----|--------|----------------|---------------------|---------------------|---------------------|-----------|
| Lee SH       | Korea   | AHA/NHLBI| 2016| Both   | 63.6 - 110    | 36.45               | 8114                | 19295               | [37]      |
| Muller R     | Estonia | NCEP-ATP III| 2016| Both   | 51.6 - 66    | 35.16               | 75                  | 273                 | [33]      |
| Dihingia P   | India   | NCEP-ATP III| 2016| Both   | 41.5 - 66    | 16.66               | 72                  | 6.94                | [39]      |
| Parra-Salcedo F | Mexico | AHA/NHLBI| 2015| Both   | 38.1 - 18    | 28.12               | 18                  | 4.81                | [43]      |
| Parra-Salcedo F | Mexico | IDF   | 2015| Both   | 38.1 - 18    | 18.12               | 18                  | 4.18                | [43]      |
| Parra-Salcedo F | Mexico | NCEP-ATP III| 2015| Both   | 38.1 - 18    | 23.75               | 18                  | 4.31                | [43]      |
| Bilecik NA   | Turkey  | IDF     | 2014| Female | 52.0 - 24–65| 33.0                | 100                 | 44.0                | [44]      |
| Bilecik NA   | Turkey  | NCEP-ATP III| 2014| Female | 52.0 - 24–65| 27.0                | 100                 | 28.0                | [44]      |
| Özmen M      | Turkey  | NCEP-ATP III| 2014| Both   | 51.0 - 15    | 17.30               | 9                   | 6.60                | [45]      |
| Kumar BS     | India   | IDF     | 2014| Both   | 46.0 - 6     | 31.48               | 6                   | 24.07               | [46]      |
| Kumar BS     | India   | NCEP-ATP III| 2014| Both   | 46.0 - 6     | 29.62               | 6                   | 22.22               | [46]      |
| Abourazzak FE | Morocco | IDF   | 2014| Both   | 49.0 - 22    | 30.72               | 23                  | 5.36                | [26]      |
| Abourazzak FE | Morocco | NCEP-ATP III| 2014| Both   | 49.0 - 22    | 29.05               | 23                  | 5.36                | [26]      |
| Abourazzak FE | Morocco | AACE 2003| 2014| Both   | 49.0 - 22    | 24.58               | 23                  | 7.38                | [26]      |
| Salinas MJH  | Argentina | ATP III| 2013| Both   | 55.5 - 69    | 30.31               | 103                 | 39.90               | [47]      |
| Salinas MJH  | Argentina | IDF   | 2013| Both   | 55.5 - 69    | 35.45               | 103                 | 40.54               | [47]      |
| Chung CP     | Usa     | NCEP-ATP III| 2008| Both   | 59.0 - 43–59| 42.42               | 50                  | 22.35               | [29]      |
| Dao HH       | Vietnam | WHO     | 2010| Female | 56.3 - 26–73| 19.04               | 56                   | 12.35               | [57]      |
| Dao HH       | Vietnam | IDF     | 2010| Female | 56.3 - 26–73| 40.95               | 56                   | 22.85               | [57]      |
| Dao HH       | Vietnam | NCEP-ATP III| 2010| Female | 56.3 - 26–73| 24.76               | 56                   | 14.28               | [57]      |
| Dao HH       | Vietnam | NCEP-ATP III| 2010| Female | 56.3 - 26–73| 32.38               | 56                   | 18.09               | [57]      |
| Dao HH       | Vietnam | EGIR    | 2010| Female | 56.3 - 26–73| 16.19               | 56                   | 10.47               | [57]      |
| Dao HH       | Vietnam | JS2009  | 2010| Female | 56.3 - 26–73| 32.38               | 56                   | 18.09               | [57]      |
| Karimi M     | Iran    | NCEP-ATP III| 2011| Both   | 48.3 - 92    | 27.17               | 96                  | 35.41               | [22]      |
| Rostam S     | Morocco | WHO     | 2013| Both   | 49.0 - 10    | 20.00               | 10                   | 14.00               | [49]      |
| Rostam S     | Morocco | IDF     | 2013| Both   | 49.0 - 10    | 48.60               | 10                   | 23.00               | [49]      |
| Rostam S     | Morocco | NCEP-ATP III| 2013| Both   | 49.0 - 10    | 24.16               | 10                   | 16.00               | [49]      |
| Rostam S     | Morocco | NCEP-ATP III| 2013| Both   | 49.0 - 10    | 32.50               | 10                   | 18.0                | [49]      |

(Continued)
| First Author | Country | Criteria | DOP     | Gender | N. RA Patients | N. Healthy Controls | Reference |
|--------------|---------|----------|---------|--------|----------------|---------------------|-----------|
| Rostam S     | Morocco | EGIR     | 2013    | Both   | 49.0-10       | 110/120             | 18.33     | 48.5-10  | 10/90   | 100/12.00 | [49] |
| Rostam S     | Morocco | JS2009   | 2013    | Both   | 49.0-10       | 110/120             | 32.50     | 48.5-10  | 10/90   | 100/18.0 | [49] |
| Crowson CS   | USA     | NCEP-ATP III | 2011 | Both   | 58.8-58       | 174/232             | 32.75     | 63.9-56  | 681/1241| 25.46   | [31] |
| Cunha VR     | Brazil  | NCEP-ATP III | 2012 | Both   | 56.8-50       | 233/283             | 39.22     | 44.5-34  | 192/226 | 19.46   | [53] |
| Giles JT     | USA     | NCEP-ATP III | 2010 | Both   | 61.0-51       | 131/192             | 35.87     | 63.0-70  | 51/121  | 25.61   | [60] |
| Sahebari M   | Iran    | NCEP-ATP III | 2011 | Both   | 45.5-14       | 106/120             | 45.0      | 45.6-69  | 431/500 | 53.8    | [55] |
| Sahebari M   | Iran    | IDF      | 2011    | Both   | 45.5-14       | 106/120             | 30.83     | 45.6-69  | 431/500 | 34.2    | [55] |
| Karakoc M    | Turkey  | IDF      | 2012    | Both   | 49.7-7        | 47/54               | 42.59     | 47.0-43  | 9/52    | 9.61    | [51] |
| Santos MJ    | Portugal| ATP III  | 2010    | Female  | 49.2-0       | 98/98               | 24.48     | 47.7-0   | 102/102 | 15.68   | [61] |
| Mok CC       | Hong Kong | JS2009   | 2011    | Both   | 53.3-133      | 566/699             | 19.59     | 52.9-266 | 1132/1398| 19.88  | [56] |
III. IDF and AACE) the prevalence of MetS in RA patients varied from 24.6 to 30.7% [26].

Finally, the results of a case-control study in 2013 showed that the frequency of MetS in RA patients and the control group were 30% versus 39% (respectively) when using the ATP III definition and 35% versus 40% (respectively) when using the IDF definition [27].

Fig 6. Forest plot of MetS risk among RA patients by definition/criteria.

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III, IDF and AACE) the prevalence of MetS in RA patients varied from 24.6 to 30.7% [26].

Finally, the results of a case-control study in 2013 showed that the frequency of MetS in RA patients and the control group were 30% versus 39% (respectively) when using the ATP III definition and 35% versus 40% (respectively) when using the IDF [27] definition.
Therefore, it appears that some of the variation in the prevalence reported are to do with i) a lack of definition clarity, with many different criteria in the existing definitions, ii) different and multiple phenotypes included in each definition of MetS, and iii) the lack of consistency in the number of components required by each definition.

However, prevalence rates also vary widely even when comparing studies that have used the same criteria. For example, using the NCE/ATP definition, Dessein et al. reported a MetS prevalence of 19% among 74 RA patients [28], while a separate study using the same definition reported a prevalence rate of 42% in those with long standing RA and 30% in those recently diagnosed with RA[29]. Further, in a study of 107 female RA patients a MetS prevalence of 18.7% [30] was reported, but using the same definition Crowson et al. reported the prevalence to be 33%[31]. Therefore, it is likely that other factors related to the characteristics of the study population, such as: genetic, ethnic, cultural, demographic, socioeconomic and clinical factors, also affect the prevalence. Thus, studies conducted using different populations are critical in order to identify other factors related to MetS.

In this study the risk of MetS in RA patients was 45% higher than that in the healthy control group (OR = 1.45; 95% CI: 1.20–1.75). The OR found in the present study is considerably higher than that reported in a meta-analysis of 12 studies in 2013, which reported an OR of 1.24 (95% CI, 1.03–1.50) [11]. Furthermore, Karvounaris et al. found prevalence of MetS to be similar in RA patients (44%) to their control population (41%), but they also found a relationship between disease activity and the presence of MetS [32]. It is also worth mentioning that several studies have not reported any association between RA and MetS [33, 34].

When we assessed the individual components of MetS (FBS, HDL, BP, Triglyceride, WC), a high WC had the highest prevalence, while the lowest prevalence was high FBS. These findings are consistent with a cross-sectional study by Zafar et al., which found that high FBS (21.9%) was the least prevalent component, while a high WC (46.1%) was the most prevalent component[35]. Furthermore, a study of 200 rheumatoid arthritis outpatients reported that the prevalence of a high WC was 74.8% in female patients and 60.4% in male patients, while the prevalence of high FBS were 30.6% and 26.4% in female and male patients, respectively [32].
In another study, blood pressure, hypoglycemia and HDL had prevalence’s of 35.9%, 22.95 and 68.9%, respectively [36]. Therefore, it seems that in most studies a high WC is the most prevalent MetS component and targeting preventative measures at this may considerably reduce the risk of developing MetS.

**Advantages**

The present study has a number of advantages over the previous meta-analysis, including: 1) All of the published studies were included in this meta-analysis. 2) The prevalence of metabolic syndrome was investigated in RA patients from across the world. 3) This study reported the prevalence of MetS in RA patients based upon eight separate definitions. 4) This paper included both comparative cross-sectional and cross-sectional studies. 5) The odds ratio for metabolic syndrome was pooled across a large number of studies.

**Limitations**

1) Several countries have not assessed the prevalence of MetS in RA patients and therefore data from those countries could not be presented in this study. 2) The crude (unadjusted) odds ratio for MetS in RA patients was reported, as different studies used different set(s) of confounders.

**Conclusion**

The prevalence of MetS in RA patients was relatively high, but did not vary significantly by gender. According to the high prevalence of MetS in RA patients and the high risk of it, monitoring and testing for metabolic syndrome in these patients is clearly recommended. As the most important component of metabolic syndrome was found to be a high WC, it is clearly important to pay more attention to patient nutrition and weight loss. Finally, mean age and the diagnostic criteria used to diagnose MetS were identified as sources of heterogeneity in the estimated risk of MetS.

**Supporting information**

S1 Appendix. (TIFF)
S2 Appendix. (TIFF)
S3 Appendix. (TIFF)
S4 Appendix. (TIFF)
S5 Appendix. (TIFF)

**Author Contributions**

Conceptualization: SS JH.
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