PLOS ONE

RESEARCH ARTICLE

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

Jamal Hallajzadeh[1,2], Saeid Safiri[2,3☯]*, Mohammad Ali Mansournia[3], Maliheh Khoramdad[4], Neda Izadi[5], Amir Almasi-Hashiani[6], Reza Pakzad[7], Erfan Ayubi[8], Mark J. M. Sullman[9], Nahid Karamzad[10☯]*

1 Department of Community Nutrition, Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran, **2** Managerial Epidemiology Research Center, Department of Public Health, School of Nursing and Midwifery, Maragheh University of Medical Sciences, Maragheh, Iran, **3** Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran, **4** Department of Epidemiology and Biostatistics, Faculty of Health, Kermanshah University of Medical Sciences, Kermanshah, Iran, **5** Department of Epidemiology, School of Public Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran, **6** Department of Epidemiology and Reproductive Health, Reproductive Epidemiology Research Centre, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran, **7** Department of Epidemiology, Faculty of Health, Ilam University of Medical Sciences, Ilam, Iran, **8** Department of Public Health, School of Public Health, Zabol University of Medical Sciences, Zabol, Iran, **9** Driving Research Group, Cranfield University, Bedfordshire, United Kingdom, **10** Vice-Chancellery for Food and Drug, Maragheh University of Medical Sciences, Maragheh, Iran

☯ These authors contributed equally to this work.
* saeidsafiri@gmail.com (SS); nahidkaramzad@gmail.com (NK)

Check for updates

OPEN ACCESS

Citation: Hallajzadeh J, Safiri S, Mansournia MA, Khoramdad M, Izadi N, Almasi-Hashiani A, et al. (2017) Metabolic syndrome and its components among rheumatoid arthritis patients: A comprehensive updated systematic review and meta-analysis. PLoS ONE 12(3): e0170361. https://doi.org/10.1371/journal.pone.0170361

Editor: Hassan Ashktorab, Howard University, UNITED STATES

Received: October 25, 2016

Accepted: January 3, 2017

Published: March 23, 2017

Copyright: © 2017 Hallajzadeh et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are available in the manuscript.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

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 (women	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	WC ≥ 102 cm (men), WC ≥ 88 cm (women	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 mmHg or previous hypertension diagnosis	≥ 130/85 or treatment	≥ 130/85 or treatment
Dyslipidmia:								
HDL-C	≥ 35 mg/dL (0.9 mmol/L) in men or ≥ 39 mg/dL (≥ 1.0 mmol/L) in women	≥ 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	≥ 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	≥ 40 mg/dL (1.03 mol/L) in men, ≥ 50 mg/dL (1.29 mmol/L) in women	≥ 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)	≥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)	≥150 mg/dL (1.7 mmol/L) or treatment
Glucose Intolerance or Fasting Plasma Glucose	≥110 mg/dL (6.1 mmol/l), DM, IGT, IR	≥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)	≥110 mg/dL (6.1 mmol/l), or treatment	≥100 mg/dL (5.6 mmol/L) or T2D	≥110 mg/dL (6.1 mmol/L)	≥100 mg/dL (5.6 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 ATPIII = 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.

https://doi.org/10.1371/journal.pone.0170361.t001

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

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

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.

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).

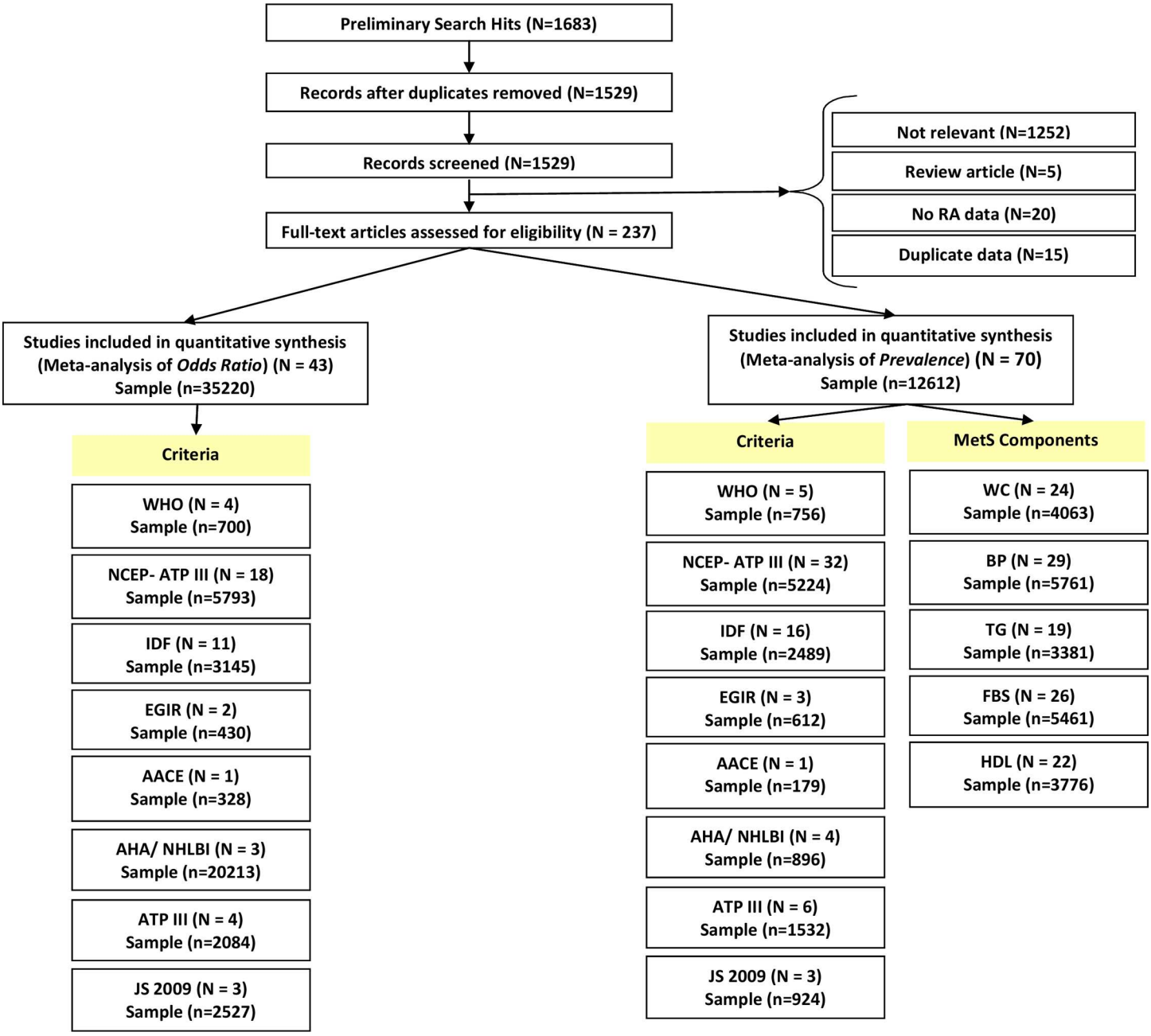

Fig 1. Flow diagram of the study selection process.

https://doi.org/10.1371/journal.pone.0170361.g001

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/NHBI**—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	110	488	36.4	34.5	36.9	[37]
Hugo M	France	IDF	2016	18–75	57.6	Both	57	15	42	24.0	25.0	24.0	[38]
Zafar ZA	Pakistan	NCEP-ATP III	2016	20–60	43.8	Both	384	97	277	31.3	18.5	35.5	[35]
Oliveira BMGB	Brazil	NCEP-ATP III	2016	-	55.5	Female	107	-	107	51.4	-	51.4	[24]
Oliveira BMGB	Brazil	IDF	2016	-	55.5	Female	107	-	107	53.4	-	53.4	[24]
Muller R	Estonia	NCEP-ATP III	2016	-	51.6	Both	91	66	25	35			[33]
Dihingia P	India	NCEP-ATP III	2016	>12	41.5	Both	72	6	66	16.7			[39]
Ghazaly AHAH	Egypt	ATP III	2015	≥18	40.7	Both	80	13	67	50.0	53.8	49.2	[40]
Salamon L	Croatia	ATP III	2015	52–68	59	Both	583	100	483	43.1	40.0	43.7	[41]
Tanayakom P	Thailand	NCEP-ATP III	2015	-	59	Both	267	31	236	16.1	12.9	16.5	[42]
Parra-Salcedo F	Mexico	AHA/NHLBI	2015	-	38.1	Both	160	18	142	28.0			[43]
Parra-Salcedo F	Mexico	IDF	2015	-	38.1	Both	160	18	142	18.0			[43]
Parra-Salcedo F	Mexico	NCEP-ATP III	2015	-	38.1	Both	160	18	142	24.0			[43]
Craciun L	Romania	IDF-AHA	2014	32–79	55.2	Both	51	7	77	19.0	10.52	82.47	[23]
Craciun L	Romania	NCEP-ATP III	2014	32–79	55.2	Both	51	7	77	23.0			[23]
Craciun L	Romania	IDF	2014	32–79	55.2	Both	51	7	77	18.0			[23]
Craciun L	Romania	AHA	2014	32–79	55.2	Both	51	7	77	14.0			[23]
Bilecik NA	Turkey	IDF	2014	24–65	52.0	Female	100	-	100	33.0	-	33.0	[44]
Bilecik NA	Turkey	NCEP-ATP III	2014	24–65	52.0	Female	100	-	100	27.0	-	27.0	[44]
Özmen M	Turkey	NCEP-ATP III	2014	-	51.0	Both	52	15	37	17.30			[45]
Özmen M	Turkey	WHO	2014	-	51.0	Both	52	15	37	28.80			[45]
Kumar BS	India	IDF	2014	≥18	46.0	Both	54	6	48	29.0			[46]
Kumar BS	India	NCEP-ATP III	2014	≥18	46.0	Both	54	6	48	31.0			[46]
Abourazzak FE	Morocco	IDF	2014	>16	49.0	Both	179	22	157	30.7			[26]
Abourazzak FE	Morocco	NCEP-ATP III	2014	>16	49.0	Both	179	22	157	29.0			[26]
Abourazzak FE	Morocco	AACE 2003	2014	>16	49.0	Both	179	22	157	24.6			[26]
Salinas MJH	Argentina	ATP III	2013	-	55.5	Both	409	69	340	30.0	62.0	23.8	[47]
Salinas MJH	Argentina	IDF	2013	-	55.5	Both	409	69	340	35.0			[47]
Abdul-Qahar	Iraq	NCEP-ATP III	2013	-	46.9	Both	203	41	162	51.2	12.0	92.0	[48]
Rostam S	Morocco	NCEP-ATP III-2004	2013	-	49.0	Both	120	10	110	30.8	10.0	32.7	[49]
Rostam S	Morocco	NCEP-ATP III-2001	2013	-	49.0	Both	120	10	110	24.6			[49]
Rostam S	Morocco	WHO	2013	-	49.0	Both	120	10	110	20.0			[49]
Rostam S	Morocco	IDF	2013	-	49.0	Both	120	10	110	48.6			[49]
Rostam S	Morocco	EGIR	2013	-	49.0	Both	120	10	110	18.0			[49]
Rostam S	Morocco	JC 2009	2013	-	49.0	Both	120	10	110	32.3			[49]
Lee SG	Korea	NCEP-ATP III	2013	22–76	50.6	Female	84	-	84	19.0	-	19.0	[34]
Ormseth MJ	USA	ATP III	2013	≥18	54.0	Both	162	18	144	36.0			[50]
Karakoc	Turkey	IDF	2012	-	49.8	Both	54	7	47	42.6			[51]
Manka V	Slovakia	IDF	2012	≥18	58.8	Both	87	4	83	48.3			[52]
Manka V	Slovakia	NCEP-ATP III	2012	≥18	58.8	Both	87	4	83	44.8			[52]
Manka V	Slovakia	AHA/NHLBI	2012	≥18	58.8	Both	87	4	83	47.1			[52]
Cunha VR Da	Brazil	NCEP-ATP III	2012	≥18	56.8	Both	283	50	233	39.2			[53]
Goshayeshi L	Iran	NCEP-ATP III	2012	-	45.5	Both	120	14	106	45.2			[21]
Bkaer JF	USA	IDF	2012	18–85	49.5	Both	499	83	416	10.6			[54]

(*Continued*)

Table 2. (*Continued*)

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	
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	≥18	48.3	Female	92	-	92	19.6	-	19.6	[22]
Mok CC	Hong Kong	JS 2009	2011	≥18	53.3	Both	699	133	566	20.0			[56]
Dao HH	Vietnam	IDF	2010	26–73	56.3	Female	105	-	105	40.9	-	40.9	[57]
Dao HH	Vietnam	NCEP-ATP III 2004	2010	26–73	56.3	Female	105	-	105	32.4	-	32.4	[57]
Dao HH	Vietnam	NCEP-ATP III 2001	2010	26–73	56.3	Female	105	-	105	24.7	-	24.7	[57]
Dao HH	Vietnam	JS 2009	2010	26–73	56.3	Female	105	-	105	32.4	-	32.4	[57]
Dao HH	Vietnam	WHO	2010	26–73	56.3	Female	105	-	105	19.0	-	19.0	[57]
Dao HH	Vietnam	EGIR	2010	26–73	56.3	Female	105	-	105	16.2	-	16.2	[57]
Raterman H G	Netherlands	NCEP	2010	50–75	62.1	Both	236	79	157	19.9			[58]
Solomon A	South Africa	NCEP-ATP III	2010	-	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	61	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	2009	55.5–69.6	63.1	Both	387	105	282	40.1	42.5	39.2	[25]
Toms TE	UK	NCEP-ATP III 2001	2009	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-Nacach 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]

https://doi.org/10.1371/journal.pone.0170361.t002

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, 29, 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

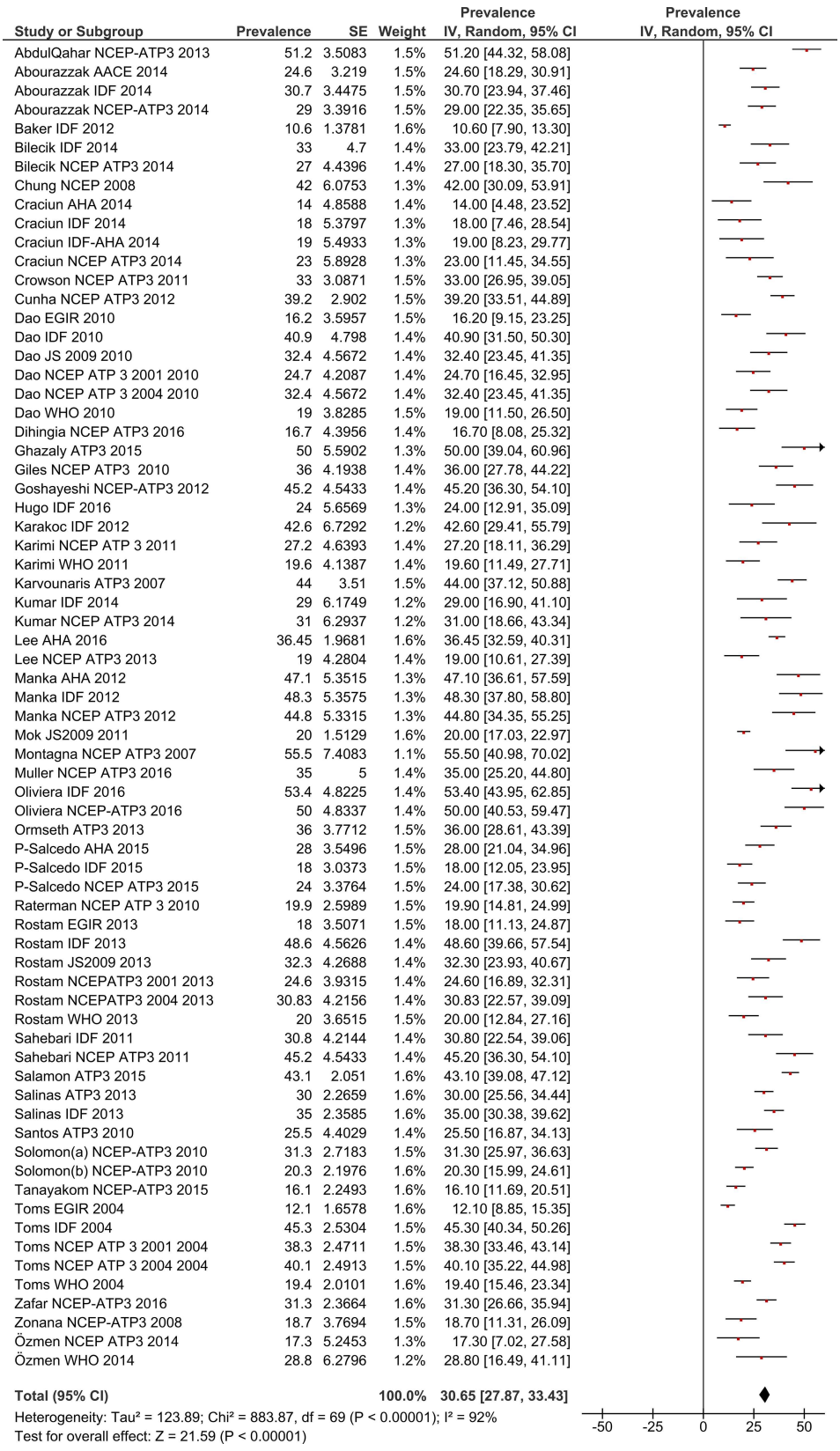

Fig 2. Forest plot of MetS prevalence in RA Patients.

https://doi.org/10.1371/journal.pone.0170361.g002

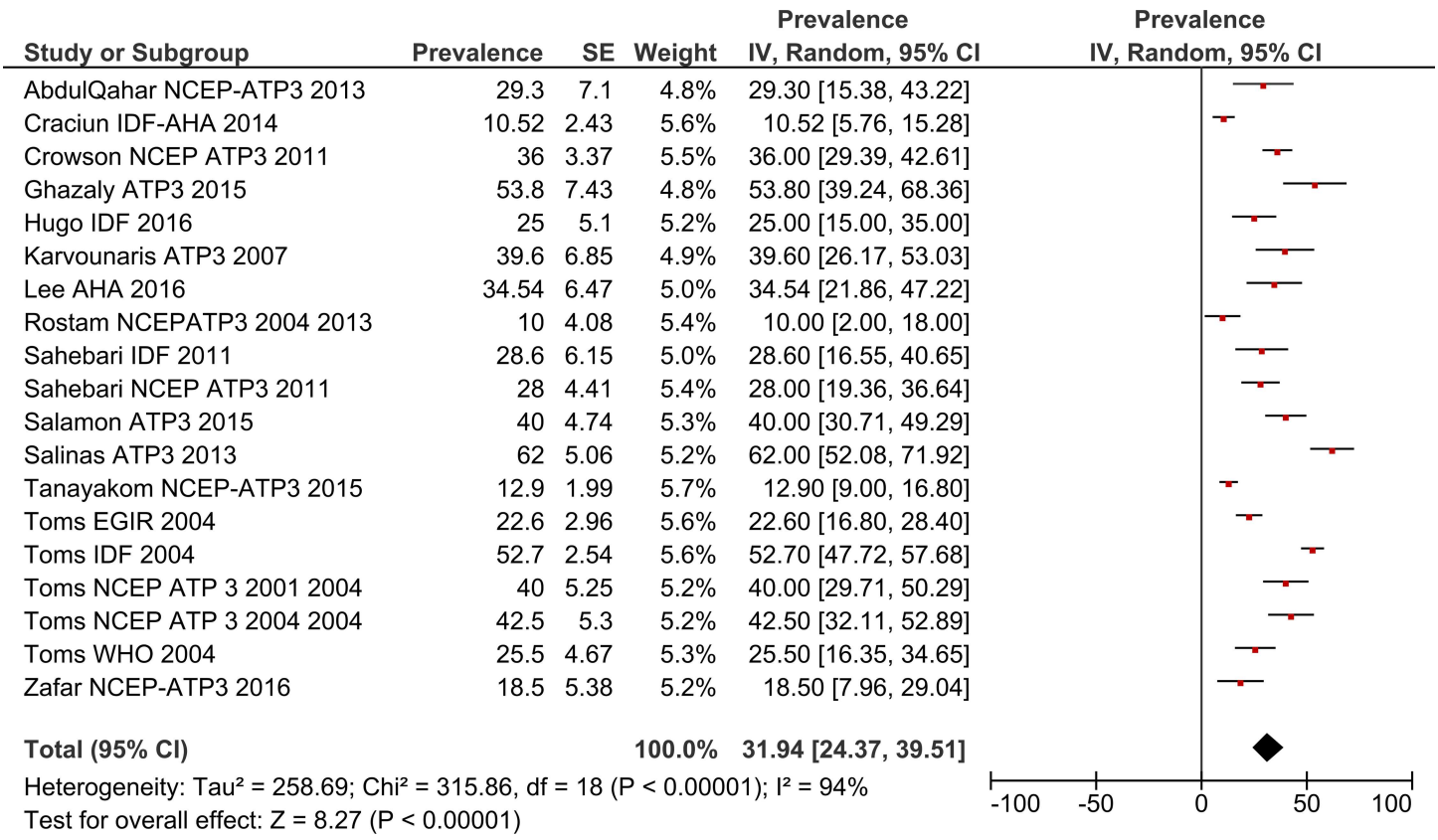

Fig 3. Forest plot of MetS prevalence among male RA Patients.

https://doi.org/10.1371/journal.pone.0170361.g003

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

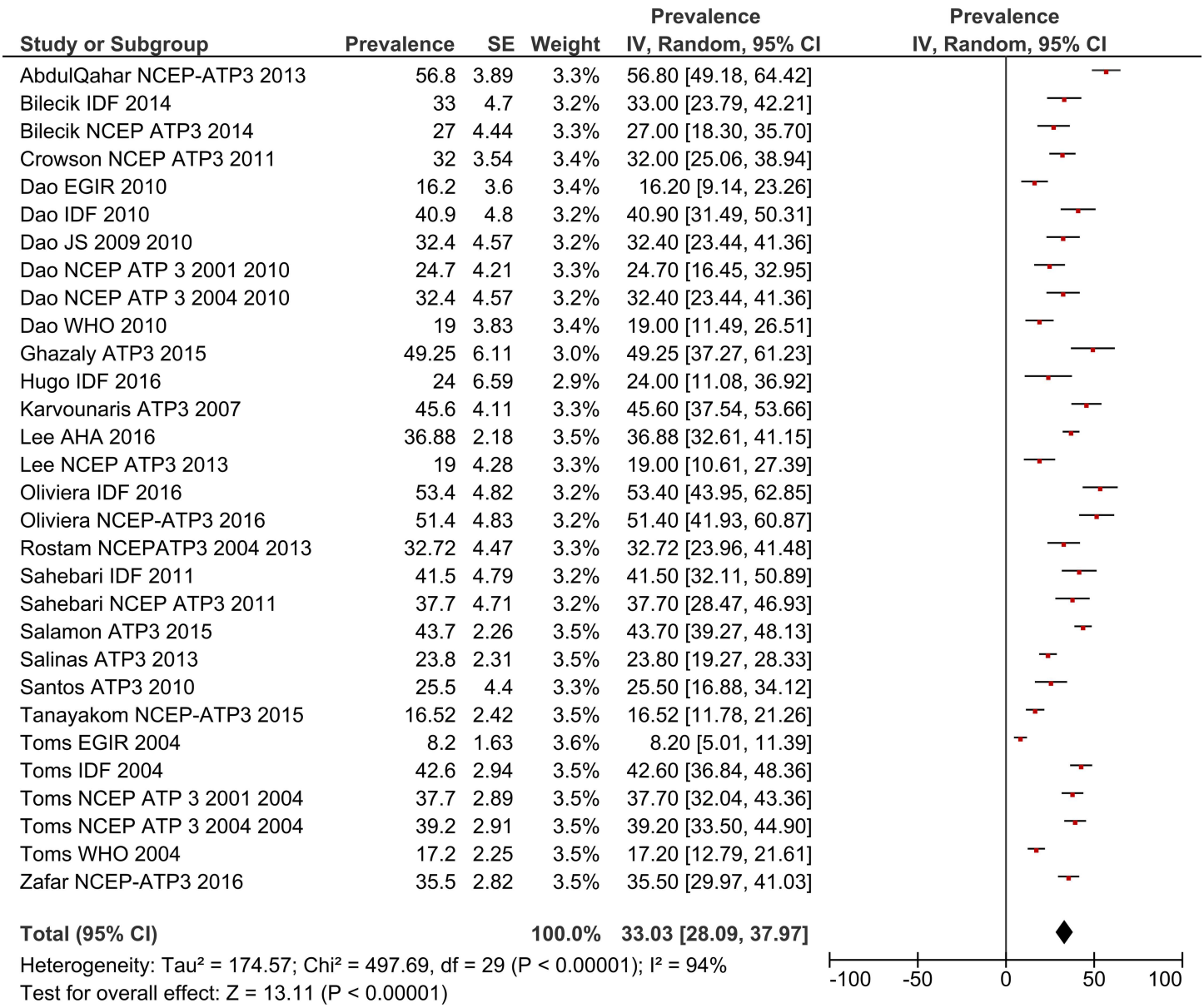

Fig 4. Forest plot of MetS prevalence among female RA Patients.

https://doi.org/10.1371/journal.pone.0170361.g004

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 NCE-P-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

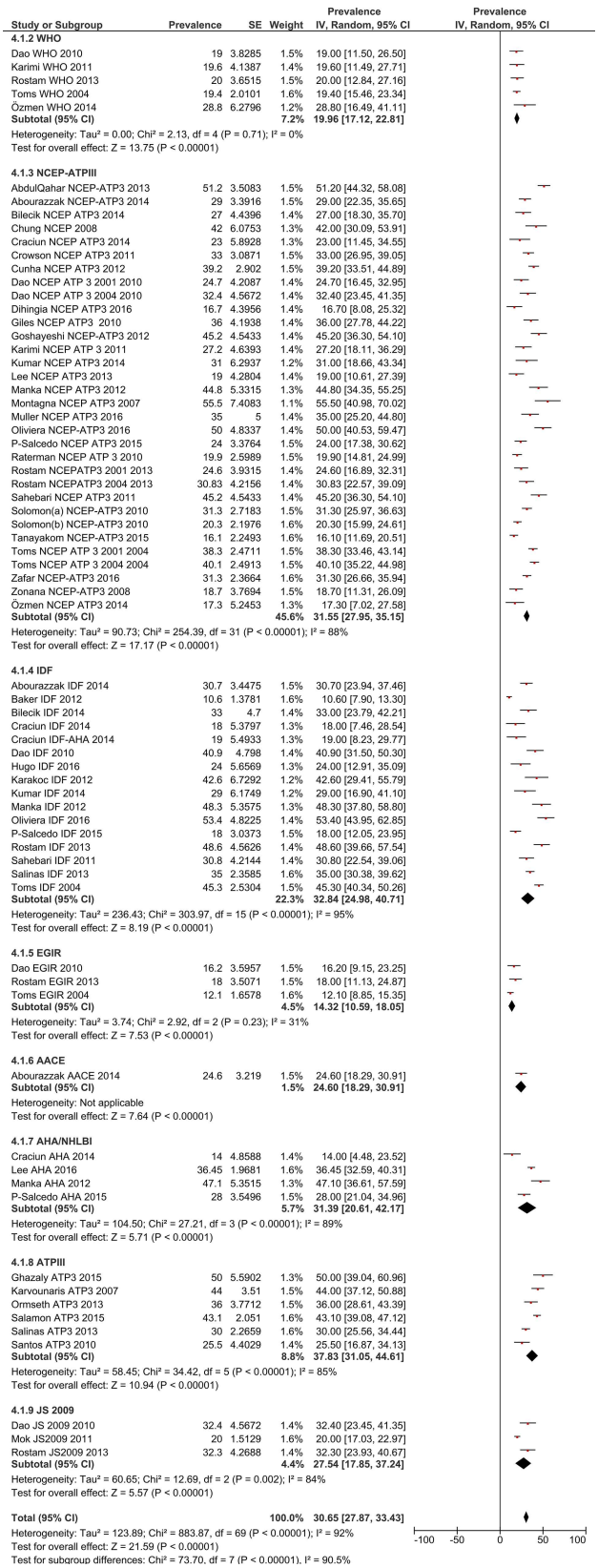

Fig 5. Forest plot of MetS prevalence among RA Patients by definition/criteria.

https://doi.org/10.1371/journal.pone.0170361.g005

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						N. Healthy Controls						Reference
					Mean Age	Age Range	Male	Female	Total		Mean Age	Age Range	Male	Female	Total		
									N.	MetS Prev. (%)					N.	MetS Prev. (%)	
Lee SH	Korea	AHA/NHLBI	2016	Both	63.6	-	110	488	598	36.45	58.4	-	8114	11181	19295	34.45	[37]
Muller R	Estonia	NCEP-ATP III	2016	Both	51.6	-	66	25	91	35.16	51.5	-	75	198	273	34.06	[33]
Dihingia P	India	NCEP-ATP III	2016	Both	41.5	-	6	66	72	16.66	-	-	-	-	72	6.94	[39]
Parra-Salcedo F	Mexico	AHA/NHLBI	2015	Both	38.1	-	18	142	160	28.12	38.0	-	18	142	160	4.81	[43]
Parra-Salcedo F	Mexico	IDF	2015	Both	38.1	-	18	142	160	18.12	38.0	-	18	142	160	4.18	[43]
Parra-Salcedo F	Mexico	NCEP-ATP III	2015	Both	38.1	-	18	142	160	23.75	38.0	-	18	142	160	4.31	[43]
Bilecik NA	Turkey	IDF	2014	Female	52.0	24–65	0	100	100	33.0	51.0	27–65	0	100	100	44.0	[44]
Bilecik NA	Turkey	NCEP-ATP III	2014	Female	52.0	24–65	0	100	100	27.0	51.0	27–65	0	100	100	28.0	[44]
Özmen M	Turkey	NCEP-ATP III	2014	Both	51.0	-	15	37	52	17.30	48.0	-	9	21	30	6.60	[45]
Özmen M	Turkey	WHO	2014	Both	51.0	-	15	37	52	28.84	48.0	-	9	21	30	10.0	[45]
Kumar BS	India	IDF	2014	Both	46.0	-	6	48	54	31.48	45.4	-	6	48	54	24.07	[46]
Kumar BS	India	NCEP-ATP III	2014	Both	46.0	-	6	48	54	29.62	45.4	-	6	48	54	22.22	[46]
Abourazzak FE	Morocco	IDF	2014	Both	49.0	-	22	157	179	30.72	51.0	-	23	126	149	5.36	[26]
Abourazzak FE	Morocco	NCEP-ATP III	2014	Both	49.0	-	22	157	179	29.05	51.0	-	23	126	149	5.36	[26]
Abourazzak FE	Morocco	AACE 2003	2014	Both	49.0	-	22	157	179	24.58	51.0	-	23	126	149	7.38	[26]
Salinas MJH	Argentina	ATP III	2013	Both	55.5	-	69	340	409	30.31	57.3	-	103	521	624	39.90	[47]
Salinas MJH	Argentina	IDF	2013	Both	55.5	-	69	340	409	35.45	57.3	-	103	521	624	40.54	[47]
Chung CP	Usa	NCEP-ATP III	2008	Both	59.0	43–59	18	48	66	42.42	52.0	44–58	30	55	85	22.35	[29]
Dao HH	Vietnam	WHO	2010	Female	56.3	26–73	0	105	105	19.04	55.7	25–72	56	49	105	12.35	[57]
Dao HH	Vietnam	IDF	2010	Female	56.3	26–73	0	105	105	40.95	55.7	25–72	56	49	105	22.85	[57]
Dao HH	Vietnam	NCEP-ATP III	2010	Female	56.3	26–73	0	105	105	24.76	55.7	25–72	56	49	105	14.28	[57]
Dao HH	Vietnam	NCEP-ATP III	2010	Female	56.3	26–73	0	105	105	32.38	55.7	25–72	56	49	105	18.09	[57]
Dao HH	Vietnam	EGIR	2010	Female	56.3	26–73	0	105	105	16.19	55.7	25–72	56	49	105	10.47	[57]
Dao HH	Vietnam	JS2009	2010	Female	56.3	26–73	0	105	105	32.38	55.7	25–72	56	49	105	18.09	[57]
Karimi M	Iran	NCEP-ATP III	2011	Both	48.3	-	-	-	92	27.17	42.2	-	-	-	96	35.41	[22]
Rostam S	Morocco	WHO	2013	Both	49.0	-	10	110	120	20.00	48.5	-	10	90	100	14.00	[49]
Rostam S	Morocco	IDF	2013	Both	49.0	-	10	110	120	48.60	48.5	-	10	90	100	23.00	[49]
Rostam S	Morocco	NCEP-ATP III	2013	Both	49.0	-	10	110	120	24.16	48.5	-	10	90	100	16.00	[49]
Rostam S	Morocco	NCEP-ATP III	2013	Both	49.0	-	10	110	120	32.50	48.5	-	10	90	100	18.0	[49]

(*Continued*)

Table 3. (*Continued*)

First Author	Country	Criteria	DOP	Gender	N. RA Patients						N. Healthy Controls						Reference
					Mean Age	Age Range	Male	Female	Total		Mean Age	Age Range	Male	Female	Total		
									N.	MetS Prev. (%)					N.	MetS Prev. (%)	
Rostam S	Morocco	EGIR	2013	Both	49.0	-	10	110	120	18.33	48.5	-	10	90	100	12.00	[49]
Rostam S	Morocco	JS2009	2013	Both	49.0	-	10	110	120	32.50	48.5	-	10	90	100	18.0	[49]
Crowson CS	Usa	NCEP-ATP III	2011	Both	58.8	-	58	174	232	32.75	63.9	-	560	681	1241	25.46	[31]
Cunha VR da	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	80	131	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]

https://doi.org/10.1371/journal.pone.0170361.t003

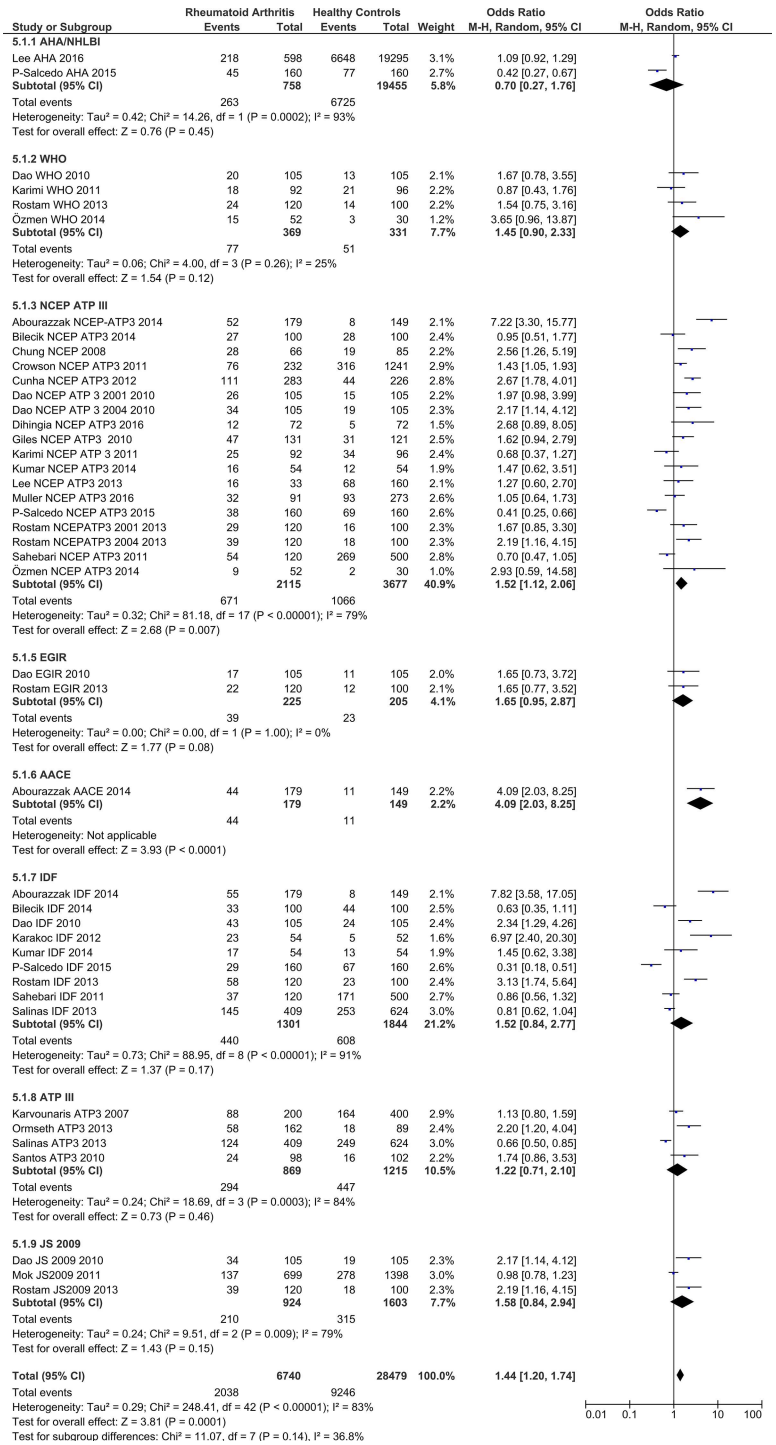

Fig 6. Forest plot of MetS risk among RA patients by definition/criteria.

https://doi.org/10.1371/journal.pone.0170361.g006

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.

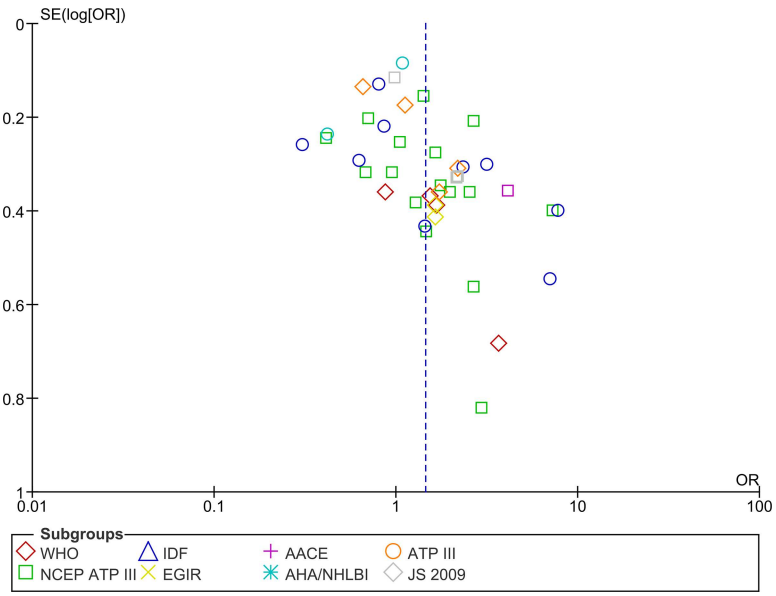

Fig 7. Funnel plot of MetS risk among RA Patients by definition/criteria.

https://doi.org/10.1371/journal.pone.0170361.g007

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.

Data curation: JH SS.

Formal analysis: SS NK.

Investigation: JH SS MAM MK NI EA AAH RP NK.

Methodology: SS NK MAM.

Project administration: JH SS.

Software: JH NK SS.

Supervision: SS.

Validation: SS.

Visualization: SS NK.

Writing – original draft: JH SS MAM MK NI MS NK EA AAH RP.

Writing – review & editing: JH SS MAM NK.

References

1. Sidiropoulos P, Karvounaris S, Boumpas D. Metabolic syndrome in rheumatic diseases: epidemiology, pathophysiology, and clinical implications. Arthritis Res Ther. 2008; 10:207. https://doi.org/10.1186/ar2397 PMID: 18492218
2. Zafar Z, H.Mahmud T, Rasheed A, AhmedWagan A. Frequency of metabolic syndrome in Pakistani cohort of patients with rheumatoid arthritis. J Pak Med Assoc. 2016; 66(6):671–6. PMID: 27339567
3. Ford E. Risks for All-Cause Mortality, Cardiovascular Disease, and Diabetes Associated With the Metabolic Syndrome A summary of the evidence. Diabetes Care. 2005; 28:1769–78. PMID: 15983333
4. Hanley A, Karter A, Williams K, et a. Prediction of type 2 diabetes mellitus with alternative definitions of the metabolic syndrome: the Insulin Resistance Atherosclerosis Study. Circulation. 2005; 112:3713–21. https://doi.org/10.1161/CIRCULATIONAHA.105.559633 PMID: 16344402
5. Mitchell AJ, Vancampfort D, Sweers K, Winkel RV, Yu W, De Hert M. Prevalence of Metabolic Syndrome and Metabolic Abnormalities in Schizophrenia and Related Disorders—A Systematic Review and Meta-Analysis. Schizophrenia Bulletin. 2013; 39(2):306–18. https://doi.org/10.1093/schbul/sbr148 PMID: 22207632
6. Ferraz-Amaro I, Gonzalez-Juanatey C, Lopez-Mejias R, Riancho-Zarrabeitia L, Gonzalez-Gay M. Metabolic syndrome in rheumatoid arthritis. Mediators Inflammation. 2013; 2013:11.
7. Tillin T, Forouhi N, DG J, et a. Metabolic syndrome and coronary heart disease in South Asians, African-Caribbeans and white Europeans: a UK population-based cross-sectional study. Diabetologia. 2005; 48:649–56. https://doi.org/10.1007/s00125-005-1689-3 PMID: 15759110
8. Hwang L, Bai C, Chen C. Prevalence of obesity and metabolic syndrome in Taiwan. J Formos Med Assoc. 2006; 105:626–35. https://doi.org/10.1016/S0929-6646(09)60161-3 PMID: 16935763
9. Kojima M, Kojima T, Ishiguro N, Oguchi T, Oba M, Tsuchiya H, et al. Psychosocial factors, disease status, and quality of life in patients with rheumatoid arthritis. J Psychosom Res. 2009; 67:425–31. https://doi.org/10.1016/j.jpsychores.2009.01.001 PMID: 19837205
10. Tierney M, Fraser A, Kennedy N. Physical activity in rheumatoid arthritis: a systematic review. J Phys Act Health. 2012; 9:1036–48. PMID: 22971883
11. Zhang J, Fu L, Shi J, Chen X, Li Y, Ma B, et al. The risk of metabolic syndrome in patients with rheumatoid arthritis: a meta-analysis of observational studies. PLoS One. 2013; 8(10):e78151. https://doi.org/10.1371/journal.pone.0078151 PMID: 24205134
12. Parra-Salcedo F, Contreras-Yáñez I, Elías-López D, Aguilar-Salinas C, Pascual-Ramos V. Prevalence, incidence and characteristics of the metabolic syndrome (MetS) in a cohort of Mexican Mestizo early rheumatoid arthritis patients treated with conventional disease modifying anti-rheumatic drugs: the complex relationship between MetS and disease activity. Arthritis research & therapy. 2015; 17:34.
13. Dąbrowski P, Majdan M. Insulin resistance and metabolic syndrome—a different image of disorders in rheumatoid arthritis and ankylosing spondylitis. Wiad Lek. 2015; 68(3):235–41. PMID: 26753206
14. Lee S, Kim J, Lee S, Kim K, Kim J, Yi J, et al. Is the frequency ofmetabolic syndrome higher in South Korean women with rheumatoid arthritis than in healthy subjects? Korean J Intern Med. 2013; 28:206–15. https://doi.org/10.3904/kjim.2013.28.2.206 PMID: 23526131

15. Dao H, Do Q, Sakamoto J. Increased frequency of metabolic syndrome among Vietnamese women with early rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther. 2010; 12:R218. https://doi.org/10.1186/ar3203 PMID: 21182767

16. Rostom S, Mengat M, Lahlou R, Hari A, Bahiri R, Hajjaj-Hassouni N. Metabolic syndrome in rheumatoid arthritis: case control study. BMC MusculoskeletDisord. 2013; 14:147.

17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009; 151(4):264–9. PMID: 19622511

18. Haddaway NR, Collins AM, Coughlin D, Kirk S. The role of Google Scholar in evidence reviews and its applicability to grey literature searching. PLOS ONE. 2015; 10(9):e0138237. https://doi.org/10.1371/journal.pone.0138237 PMID: 26379270

19. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Annals of internal medicine. 2007; 147(8):W-163-W-94.

20. Sterne JA, Harbord RM. Funnel plots in meta-analysis. Stata Journal. 2004; 4:127–41.

21. Goshayeshi L, Saber H, Sahebari M, Rezaieyazdi Z, Rafatpanah H, Esmaily H, et al. Association between metabolic syndrome, BMI, and serum vitamin D concentrations in rheumatoid arthritis. Clinical rheumatology. 2012; 31(8):1197–203. https://doi.org/10.1007/s10067-012-1995-3 PMID: 22581277

22. Karimi M, Mazloomzadeh S, Kafan S, Amirmoghadami H. The frequency of metabolic syndrome in women with rheumatoid arthritis and in controls. International journal of rheumatic diseases. 2011; 14 (3):248–54. https://doi.org/10.1111/j.1756-185X.2011.01595.x PMID: 21816020

23. Crăciun L, Crăciun P, Buicu F. Prevalence of Metabolic Syndrome in Psoriatic Arthritis and Rheumatoid Arthritis. Acta Medica Marisiensis. 2014; 60(5):196–9.

24. Oliveira BMGBd, Medeiros MMdC, Cerqueira JVMd, Quixadá RTdS, Oliveira ÍMAXd. Metabolic syndrome in patients with rheumatoid arthritis followed at a University Hospital in Northeastern Brazil. Revista brasileira de reumatologia. 2016; 56(2):117–25. https://doi.org/10.1016/j.rbre.2015.08.016 PMID: 27267524

25. Toms TE, Panoulas VF, John H, Douglas KM, Kitas GD. Methotrexate therapy associates with reduced prevalence of the metabolic syndrome in rheumatoid arthritis patients over the age of 60-more than just an anti-inflammatory effect? A cross sectional study. Arthritis research & therapy. 2009; 11(4):1.

26. Abourazzak FE, Mansouri S, Najdi A, Tahiri L, Nejjari C, Harzy T. Prevalence of metabolic syndrome in patients with rheumatoid arthritis in Morocco: a cross-sectional study of 179 cases. Clinical rheumatology. 2014; 33(11):1549–55. https://doi.org/10.1007/s10067-014-2570-x PMID: 24647982

27. Kerekes G, Nurmohamed MT, González-Gay MA, Seres I, Paragh G, Kardos Z, et al. Rheumatoid arthritis and metabolic syndrome. Nature Reviews Rheumatology. 2014; 10(11):691–6. https://doi.org/10.1038/nrrheum.2014.121 PMID: 25090948

28. Dessein PH, Tobias M, Veller MG. Metabolic syndrome and subclinical atherosclerosis in rheumatoid arthritis. The Journal of rheumatology. 2006; 33(12):2425–32. PMID: 17080519

29. Chung CP, Oeser A, Solus JF, Avalos I, Gebretsadik T, Shintani A, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis. 2008; 196(2):756–63. https://doi.org/10.1016/j.atherosclerosis.2007.01.004 PMID: 17266963

30. Zonana-Nacach A, Santana-Sahagún E, Jiménez-Balderas FJ, Camargo-Coronel A. Prevalence and factors associated with metabolic syndrome in patients with rheumatoid arthritis and systemic lupus erythematosus. JCR: Journal of Clinical Rheumatology. 2008; 14(2):74–7. https://doi.org/10.1097/RHU.0b013e31816b2faa PMID: 18391674

31. Crowson CS, Myasoedova E, Davis JM, Matteson EL, Roger VL, Therneau TM, et al. Increased prevalence of metabolic syndrome associated with rheumatoid arthritis in patients without clinical cardiovascular disease. The Journal of rheumatology. 2011; 38(1):29–35. https://doi.org/10.3899/jrheum.100346 PMID: 20952464

32. Karvounaris SA, Sidiropoulos PI, Papadakis JA, Spanakis EK, Bertsias GK, Kritikos HD, et al. Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled, study. Annals of the rheumatic diseases. 2007; 66(1):28–33. https://doi.org/10.1136/ard.2006.053488 PMID: 16793841

33. Müller R, Kull M, Põlluste K, Aart A, Eglit T, Lember M, et al. The metabolic profile in early rheumatoid arthritis: a high prevalence of metabolic obesity. Rheumatology international. 2016:1–7.

34. Lee S-G, Kim J-M, Lee S-H, Kim K-H, Kim J-H, Yi J-W, et al. Is the frequency of metabolic syndrome higher in South Korean women with rheumatoid arthritis than in healthy subjects? The Korean journal of internal medicine. 2013; 28(2):206–15. https://doi.org/10.3904/kjim.2013.28.2.206 PMID: 23526131

35. Zafar ZA, Mahmud TH, Rasheed A, Wagan AA. Frequency of metabolic syndrome in Pakistani cohort of patients with rheumatoid arthritis.

36. La Montagna G, Cacciapuoti F, Buono R, Manzella D, Mennillo GA, Arciello A, et al. Insulin resistance is an independent risk factor for atherosclerosis in rheumatoid arthritis. Diabetes and Vascular Disease Research. 2007; 4(2):130–5. https://doi.org/10.3132/dvdr.2007.031 PMID: 17654447

37. Lee S-H, Choi H, Cho B-L, An A-R, Seo Y-G, Jin H-S, et al. Relationship between Metabolic Syndrome and Rheumatoid Arthritis. Korean journal of family medicine. 2016; 37(1):44–50. https://doi.org/10.4082/kjfm.2016.37.1.44 PMID: 26885322

38. Hugo M, Mehsen-Cetre N, Pierreisnard A, Schaeverbeke T, Gin H, Rigalleau V. Energy expenditure and nutritional complications of metabolic syndrome and rheumatoid cachexia in rheumatoid arthritis: an observational study using calorimetry and actimetry. Rheumatology. 2016:kew038.

39. Dihingia P, Das D, Chakraborty A, Debbarma M, Kakati S. INCREASE FREQUENCY OF METABOLIC SYNDROME AMONG THE CASES OF RHEUMATOID ARTHRITIS: A CASE CONTROL STUDY. HYPERTENSION. 41(56.9):56.9.

40. Ghazaly AHAH, El-Moez KM, El Shorbagy MS, El-Nahrery EM. Angiopoietin-2 as a biomarker for metabolic syndrome and disease activity in rheumatoid arthritis patients. The Egyptian Rheumatologist. 2016; 38(1):9–13.

41. Šalamon L, Morović-Vergles J, Marasović-Krstulović D, Kehler T, Šakić D, Badovinac O, et al. Differences in the prevalence and characteristics of metabolic syndrome in rheumatoid arthritis and osteoarthritis: a multicentric study. Rheumatology international. 2015; 35(12):2047–57. https://doi.org/10.1007/s00296-015-3307-0 PMID: 26059944

42. Tantayakom P, Koolvisoot A, Arromdee E, Chiowchanwisawakit P, Muangchan C, Katchamart W. Metabolic syndrome is associated with disease activity in patients with rheumatoid arthritis. Joint Bone Spine. 2016.

43. Parra-Salcedo F, Contreras-Yáñez I, Elías-López D, Aguilar-Salinas CA, Pascual-Ramos V. Prevalence, incidence and characteristics of the metabolic syndrome (MetS) in a cohort of Mexican Mestizo early rheumatoid arthritis patients treated with conventional disease modifying anti-rheumatic drugs: the complex relationship between MetS and disease activity. Arthritis research & therapy. 2015; 17 (1):1.

44. Bilecik NA[1], Tuna S, Samancı N, Balcı N, Akbaş H. Prevalence of metabolic syndrome in women with rheumatoid arthritis and effective factors. International journal of clinical and experimental medicine. 2014; 7(8):2258. PMID: 25232418

45. Ozmen M, Ozturk S, Soysal D, Koseoglu M. Prevalence of the metabolic syndrome in rheumatoid arthritis. Eur J Rheumatol. 2014; 1:1–4. https://doi.org/10.5152/eurjrheum.2014.001 PMID: 27708861

46. Kumar BS, Naik GS, Mohan A, Kumar DP, Suresh V, Sarma K, et al. Prevalence of thyroid disorders and metabolic syndrome in adult patients with rheumatoid arthritis.

47. Salinas MJH, Bertoli AM, Lema L, Saucedo C, Rosa J, Quintana R, et al. Prevalence and correlates of metabolic syndrome in patients with rheumatoid arthritis in Argentina. JCR: Journal of Clinical Rheumatology. 2013; 19(8):439–43. https://doi.org/10.1097/RHU.0000000000000039 PMID: 24263146

48. Abdul-Qaharr Z, Al-Osami MH. Prevalence of Metabolic Syndrome in Iraqi Patients with Rheumatoid Arthritis. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS). 1(11):69–72.

49. Rostom S, Mengat M, Lahlou R, Hari A, Bahiri R, Hajjaj-Hassouni N. Metabolic syndrome in rheumatoid arthritis: case control study. BMC musculoskeletal disorders. 2013; 14(1):1.

50. Ormseth MJ, Lipson A, Alexopoulos N, Hartlage GR, Oeser AM, Bian A, et al. Epicardial adipose tissue is associated with cardiometabolic risk and the metabolic syndrome in patients with rheumatoid arthritis. Arthritis care & research. 2013; 65(9):1410.

51. Karakoc M, Batmaz I, Sariyildiz MAA, Tahtasiz M, Cevik R, Tekbas E, et al. The relationship of metabolic syndrome with disease activity and the functional status in patients with rheumatoid arthritis. Journal of clinical medicine research. 2012; 4(4):279–85. https://doi.org/10.4021/jocmr1001w PMID: 22870176

52. Manka V, Galajda P, Sagova I, Klimentova A, Kantarova D, Stancik M, et al. Metabolic Syndrome in Rheumatoid Arthritis. Acta Medica Martiniana. 2012; 12(3):19–27.

53. Da Cunha V, Brenol C, Brenol J, Fuchs S, Arlindo E, Melo I, et al. Metabolic syndrome prevalence is increased in rheumatoid arthritis patients and is associated with disease activity. Scandinavian journal of rheumatology. 2012; 41(3):186–91. https://doi.org/10.3109/03009742.2011.626443 PMID: 22416768

54. Baker JF, Mehta NN, Baker DG, Toedter G, Shults J, Von Feldt JM, et al. Vitamin D, metabolic dyslipidemia, and metabolic syndrome in rheumatoid arthritis. The American journal of medicine. 2012; 125 (10):1036. e9-. e15.

55. Sahebari M, Goshayeshi L, Mirfeizi Z, Rezaieyazdi Z, Hatef MR, Ghayour-Mobarhan M, et al. Investigation of the association between metabolic syndrome and disease activity in rheumatoid arthritis. The Scientific World Journal. 2011; 11:1195–205. https://doi.org/10.1100/tsw.2011.111 PMID: 21666989

56. Mok CC, Ko GTC, Ho LY, Yu KL, Chan PT, To CH. Prevalence of atherosclerotic risk factors and the metabolic syndrome in patients with chronic inflammatory arthritis. Arthritis care & research. 2011; 63 (2):195–202.

57. Dao H-H, Do Q-T, Sakamoto J. Increased frequency of metabolic syndrome among Vietnamese women with early rheumatoid arthritis: a cross-sectional study. Arthritis research & therapy. 2010; 12 (6):1.

58. Raterman H, Van Eijk I, Voskuyl A, Peters M, Dijkmans B, Van Halm V, et al. The metabolic syndrome is amplified in hypothyroid rheumatoid arthritis patients: a cross-sectional study. Annals of the rheumatic diseases. 2010; 69(01):39–42.

59. Solomon A, Christian BF, Norton GR, Woodiwiss AJ, Dessein PH. Risk factor profiles for atherosclerotic cardiovascular disease in black and other Africans with established rheumatoid arthritis. The Journal of rheumatology. 2010; 37(5):953–60. https://doi.org/10.3899/jrheum.091032 PMID: 20231201

60. Giles JT, Allison M, Blumenthal RS, Post W, Gelber AC, Petri M, et al. Abdominal adiposity in rheumatoid arthritis: association with cardiometabolic risk factors and disease characteristics. Arthritis & Rheumatism. 2010; 62(11):3173–82.

61. Santos MJ, Vinagre F, Silva J, Gil V, Fonseca J. Cardiovascular risk profile in systemic lupus erythematosus and rheumatoid arthritis: a comparative study of female patients. Acta Reumatológica Portuguesa. 2010:325–32. PMID: 20975635

62. La Montagna G, Cacciapuoti F, Buono R, Manzella D, Mennillo G, Arciello A, et al. Insulin resistance is an independent risk factor for atherosclerosis in rheumatoid arthritis. Scand J Rheumatol. 2006.