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Original Article

Association of rheumatoid arthritis and the prevalence of metabolic syndrome: an update meta-analysis

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Abstract: The aim of the study is to evaluate the association between rheumatoid arthritis (RA) and the risk of metabolic syndrome (MetS). Studies were retrieved in PubMed, Embase and Springer link databases based on predefined searching strategy and inclusion criteria. The Newcastle-Ottawa Scale was utilized to assess the quality of the studies. Odds Ratios (ORs) and 95% confidence intervals (CIs) were utilized to calculate the pooled results. Subgroup analyses were conducted to discuss whether geographic region, study type and sex composition could affect the result. Funnel plot was used to determine the potential publication bias. Seventeen studies containing 3251 RA patients and 5536 healthy controls were identified. As a result, RA patients achieved a higher prevalence of MetS than healthy controls, with the diagnostic criterion of NCEP-ATP III (OR = 1.38, 95% CI: 1.04 to 1.83, $P = 0.02$), but not with WHO or IDF criterion ($P > 0.05$). In studies that MetS was diagnosed by NCEP-ATP III criterion, subgroup analysis indicated that there was no significant association between MetS and RA, neither in study type subgroup, nor in region subgroup ($P > 0.05$). With regard to sex composition, the significant association was detected in male & female group (OR = 1.45, 95% CI: 1.01 to 2.07, $P = 0.04$), but not female group ($P > 0.05$). High prevalence of MetS was significantly related to RA, especially when MetS is diagnosed with NCEP-ATP III criterion. However, more prospective studies with larger sample size are required to confirm these results.

Keywords: Rheumatoid arthritis, metabolic syndrome, meta-analysis

Introduction

Rheumatoid arthritis (RA) is known as a frequent autoimmune disease that mainly influences joints [1]. Although substantial improvements have achieved for RA management, mortality caused by this disease is increasing [2]. In addition, RA is an inflammation-related disorder, and RA-related diseases and heart diseases are reported to share several common features involving inflammation [3]. Numerous studies have found that RA is tightly related to cardiovascular disease (CVD) [4]. The epidemiological data indicates that CVD is the predominant factor for about a half of RA-related deaths [5]. Metabolic syndrome (MetS) is a combination of factors such as obesity, hypertension and dyslipidaemia, which are implied to be associated with additional cardiovascular (CV) mortality [6]. Two major hallmarks of MetS are insulin resistance and hyperinsulinemia, and patients suffered with this syndrome are apt to develop CVD [7]. Due to the close relationship between MetS and CVD, emerging researches have been conducted to explore the potential correlation between RA and MetS; however, conflicting results are presented and prevalence of MetS in RA patients is different in different studies [8-10]. Moreover, insufficient statistical power exists in each individual study due to small sample size. Thus, a previous study using meta-analysis evaluated whether RA patients were more likely to develop MetS or not [11]. As a result, they concluded that prevalence of MetS in RA patients were higher than in non-RA patients. However, only 12 studies involving 6686 participants (2283 cases and 4403 controls) were identified in that meta-analysis and substantial heterogeneity was observed. Although subgroup-analysis

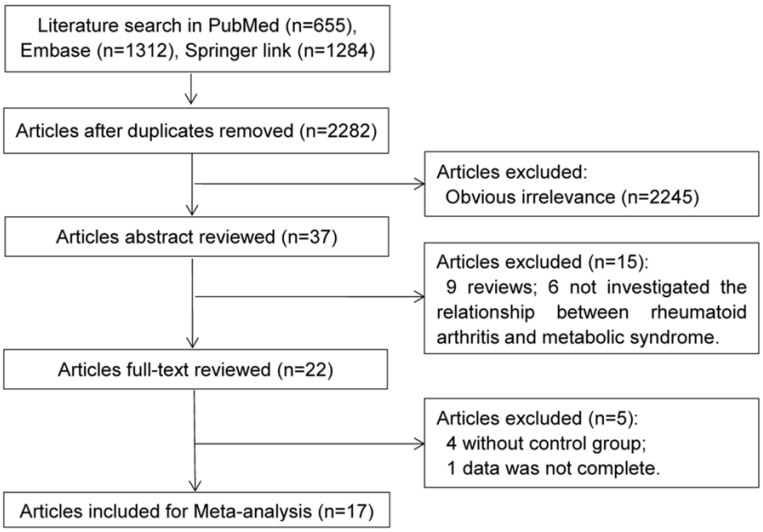

Figure 1. Procedure of study selection.

stratified by geographic region and different diagnostic criteria of MetS was concerned, study type was not considered. Additionally, all the participants in their four cross-sectional studies were female, which might cause deviations to some extent.

Therefore, we updated this meta-analysis by including more eligible studies. Moreover, study quality was assessed using a more strict system, the Newcastle-Ottawa Scale (NOS). After eligible studies were screened out, we first pooled the results according to the diagnostic criteria of MetS. Then subgroup analyses stratified by region, study type and sex composition were conducted. The study aimed to provide a more acute and reliable association between RA and the occurrence of MetS.

Materials and methods

Literature search

Literature retrieval was performed in databases such as PubMed, Embase and Springer up to January 25th 2016. The searching strategies were "metabolic syndrome" OR "MetS" AND "rheumatoid arthritis" OR "RA". Manual bibliographic search was also carried out for more eligible studies.

Study selection criteria

The studies were included if: (1) The studies were observational studies; (2) The experimental group in the study was RA patients diagnosed by American College of Rheumatology classification, while the control group was healthy individuals; (3) The studies investigated the association between RA and occurrence of MetS; (4) The studies provided odds ratios (ORs) and 95% confidence intervals (CIs) of relevant outcomes, or there were sufficient data to calculate them. On the other hand, reviews, letters or comments were excluded. If multiple studies were published basing on the same dataset or same population, only the most recent publication with complete data was included.

Data extraction and quality assessment

According to the aforementioned criteria, two authors independently completed literature search and selected eligible studies. Then based on a predefined standardized form, they independently extracted required data information from each study, such as first author information, publication year, study location, study type, sample sizes in experimental and control groups, age, sex composition and the case numbers of MetS. When there were disagreements, a discussion with a third investigator was needed to reach a consensus.

Quality of studies was evaluated using a 9-star system by NOS [12], which included a total of 8 items. A study was considered as low-, moderate- or high-quality if it achieved a score of 0-3, 4-6 or 7-9 stars, respectively.

Statistical analysis

The heterogeneity among studies was examined via Cochrane's Q-statistic and I^2 statistic [13]. If $P < 0.05$ and/or $I^2 > 50\%$, which indicates a significance, then a random-effects model is used. Otherwise, if $P \geq 0.05$ and/or $I^2 \leq 50\%$, a fixed-effects model is selected to calculate the pooled results [14]. Subgroup analyses were performed, stratified by study region, study type and sex composition, to evaluate whether these factors could influence results of this meta-analysis. Funnel plot was utilized to determine potential publication bias. The

Table 1. Characteristics of 17 included studies

Study	Year	Area	Age (ys), RA/CG	Study period (ys)	Sex	Study design	Number of RA/CG	Number of MetS-NCEP (RA/CG)	Number of MetS-WHO (RA/CG)	Number of MetS-IDF (RA/CG)
Abourazzak	2014	Morocco	49±11.5/51±13	8	M&F	CS	179/149	52/8	NA	55/16
Bilecik	2014	Turkey	52/51	NA	F	CC	100/100	27/28	NA	33/44
Chung	2008	USA	54/52	5.5	M&F	CC	154/85	54/19	55/8	NA
Crowson	2011	USA	58.8±12.8/63.9±9.2	7	M&F	CS	232/1241	76/316	NA	NA
Cunha	2012	Brazil	56.8±12.3/44.5±8.3	10.86	M&F	CC	283/226	111/44	NA	NA
Dao	2010	Viet Nam	56.3/55.7	1.75	F	CS	105/105	34/19	20/13	43/24
Karakoc	2012	Turkey	49.76±11.15/47.05±9.75	7.6	M&F	CC	54/52	NA	NA	23/5
Karimi	2011	Iran	48.3±14.6/42.2±9.9	8	F	CC	92/96	25/34	18/21	NA
Karvounaris	2006	Greece	63±11/63±11	9.52	M&F	CS	200/400	88/164	NA	NA
Lee	2013	Korea	50.6±11.3/48.3±11.3	3.5	F	CS	84/109	16/17	NA	NA
MOK	2011	Hong Kong	53.3±12.0/52.9±12.0	5.3	M&F	CC	699/1398	137/278	NA	NA
Ormseth	2013	USA	54/53	NA	M&F	CC	162/89	58/18	NA	NA
Parra-Salcedo	2015	Mexico	38.1±12.8/38.0±12.4	NA	M&F	CS	160/160	24/43	NA	18/42
Rostom	2013	Morocco	49±12/48.5±13	7.8	M&F	CC	120/100	39/18	24/14	58/23
Sahebari	2011	Iran	45.5±13/45.6±12	5.5	M&F	CC	120/500	54/269	NA	37/171
Salinas	2013	Argentina	55.5±13.2/57.3±13.1	8	M&F	CS	409/624	NA	NA	145/253
Santos	2010	Portugal	49.2±13.7/47.7±13.4	7.6	F	CC	98/102	25/16	NA	NA

Year, year of publication; ys, years; RA, rheumatoid arthritis group; CG, control group; CS, cross-sectional; CC, Case-control; M, male; F, female; NA, not available.

Table 2. Methodological quality of included studies included in the meta-analysis

Study	Selection	Comparability	Exposure	Total score
Abourazzak	☆☆☆	☆☆	☆☆	7
Bilecik	☆☆☆	☆☆	☆☆☆	8
Chung	☆☆☆☆	☆☆	☆☆☆	9
Crowson	☆☆☆	☆☆	☆☆	7
Cunha	☆☆☆	☆☆	☆☆☆	8
Dao	☆☆☆	☆☆	☆☆	7
Karakoc	☆☆	☆☆	☆☆	6
Karimi	☆☆☆	☆☆	☆☆	7
Karvounaris	☆☆☆	☆☆	☆☆	7
Lee	☆☆☆☆	☆☆	☆☆☆	9
MOK	☆☆☆	☆☆	☆☆	7
Ormseth	☆☆☆	☆☆	☆☆	7
Parra-Salcedo	☆☆☆	☆☆	☆☆	7
Rostom	☆☆☆	☆☆	☆☆	7
Sahebari	☆☆	☆☆	☆☆	6
Salinas	☆☆	☆☆	☆☆☆	7
Santos	☆☆☆	☆☆	☆☆☆	8

software RevMan 5.2 (Cochrane Collaboration, http://ims.cochrane.org/revman) was used to calculate the statistical significance.

Results

Eligible studies

Based on the aforementioned search strategy, a total of 3251 articles were retrieved via a preliminary selection, including 1312 articles in Embase database, 655 articles in PubMed database and 1284 articles in Springer link database. Then there remained 2282 articles after eliminating duplicated articles. Next, via title browsing, 2245 articles that did not meet our inclusion criteria were excluded. Thereafter, 37 articles were remained after abstract reading, among which 15 articles were further excluded due to 9 were reviews and 6 did not involve the correlation of RA and MetS. After full text reading, 5 of the 22 remaining studies were excluded. No additional studies were included by manual search. Thus, a set of 17 eligible articles were included in the meta-analysis [8-10, 15-28]. Flow chart of the study selection is shown in **Figure 1**.

Study characteristics

As presented in **Table 1**, totally, the included 17 studies consisted of 3251 RA patients in experimental group and 5536 healthy individuals in control group. The studies were published mainly from 2006 to 2015, and were primarily conducted in regions such as Europe, Asia, America and Africa. Age and sex composition of participants at study baseline had no significant differences. There are three main diagnostic criteria of MetS, including the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), the World Health Organization (WHO) and the International Diabetes Federation (IDF). According to the quality assessment results, all the studies achieved scores ≥ 6 stars, indicating a good quality of the included studies (**Table 2**).

Study outcomes

A total of 15 studies applied the diagnostic criterion of NCEP-ATP III [8, 9, 15-17, 19-28]. As shown in **Figure 2**, heterogeneity among the 15 studies was statistically significant (I^2 = 80%, P < 0.05). Therefore, the random-effects model was used. The pooled result indicated that risk of MetS diagnosed by NCEP-ATP III was significantly higher in RA patients than that in control group (OR = 1.38, 95% CI: 1.04 to 1.83, P = 0.02, **Figure 2A**).

Only 4 studies [15, 22, 25, 26] have reported the prevalence of MetSin RA patients with the WHO criterion. Likewise, a random-effects model was applied due to substantial heterogeneity across these studies (I^2 = 74%, P = 0.009), and the pooled results indicated there was no significant relationship between RA and prevalence of MetS (OR = 1.83, 95% CI: 0.88 to 3.80, P = 0.11, **Figure 2B**).

There were 8 studies reported MetS risk according to the IDF criterion [8-10, 15, 18, 20, 25, 28]. Due to substantial heterogeneity was observed among the studies (I^2 = 90%, P < 0.05), the random-effects model was selected. As a result, RA was not significantly related to MetS risk with this criterion (OR = 1.44, 95% CI: 0.81 to 2.55, P = 0.22, **Figure 2C**).

Subgroup analyses

In studies diagnosed by the NCEP-ATP III criterion, subgroup analyses stratified by study region, type and sex were performed.

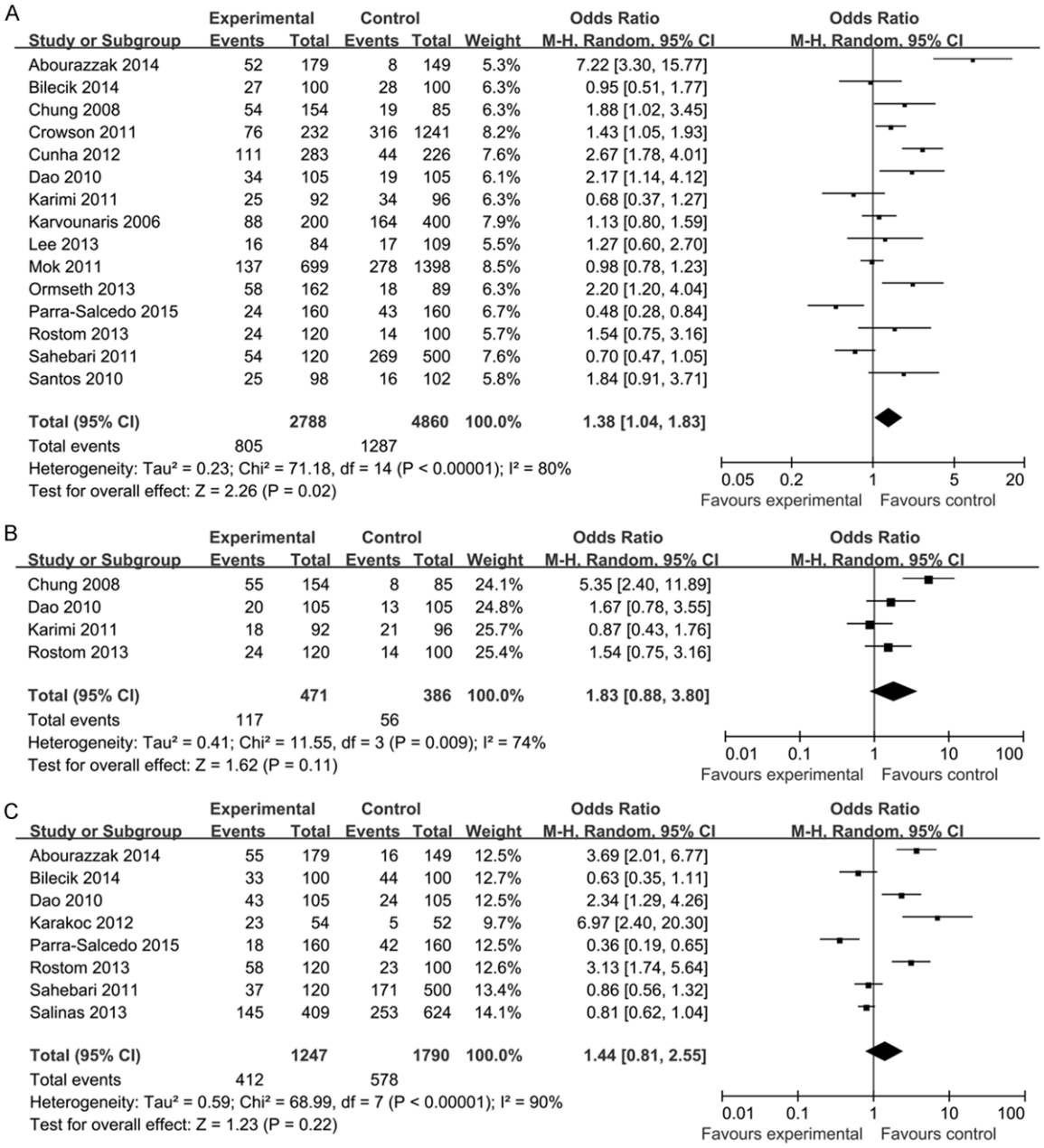

Figure 2. Forest plot of association between metabolic syndrome and rheumatoid arthritis according to different diagnostic criteria. A: With NCEP-ATP III criterion; B: With WHO criterion; C: With IDF criteria.

When stratified by study type, it indicated that cross-sectional studies and case-control studies had significant heterogeneity ($I^2 > 50\%$, $P < 0.05$), and the pooled ORs were 1.51 (95% CI: 0.88 to 2.57) and 1.32 (95% CI: 0.93 to 1.87), respectively, both without statistical significance ($P > 0.05$, **Figure 3**).

When stratified by study region, RA was not significantly associated with MetS risk in any region ($P > 0.05$, **Figure 4**).

With regard to sex, the significant association was detected in male & female group (OR = 1.45, 95% CI: 1.01 to 2.07, $P = 0.04$), but not in female group (OR = 1.25, 95% CI: 0.81 to 1.93, $P = 0.30$) (**Figure 5**).

Publication bias

The funnel plot showed that the scatter distribution was symmetrical, suggesting a lack of obvious publication bias of the included studies (**Figure 6**).

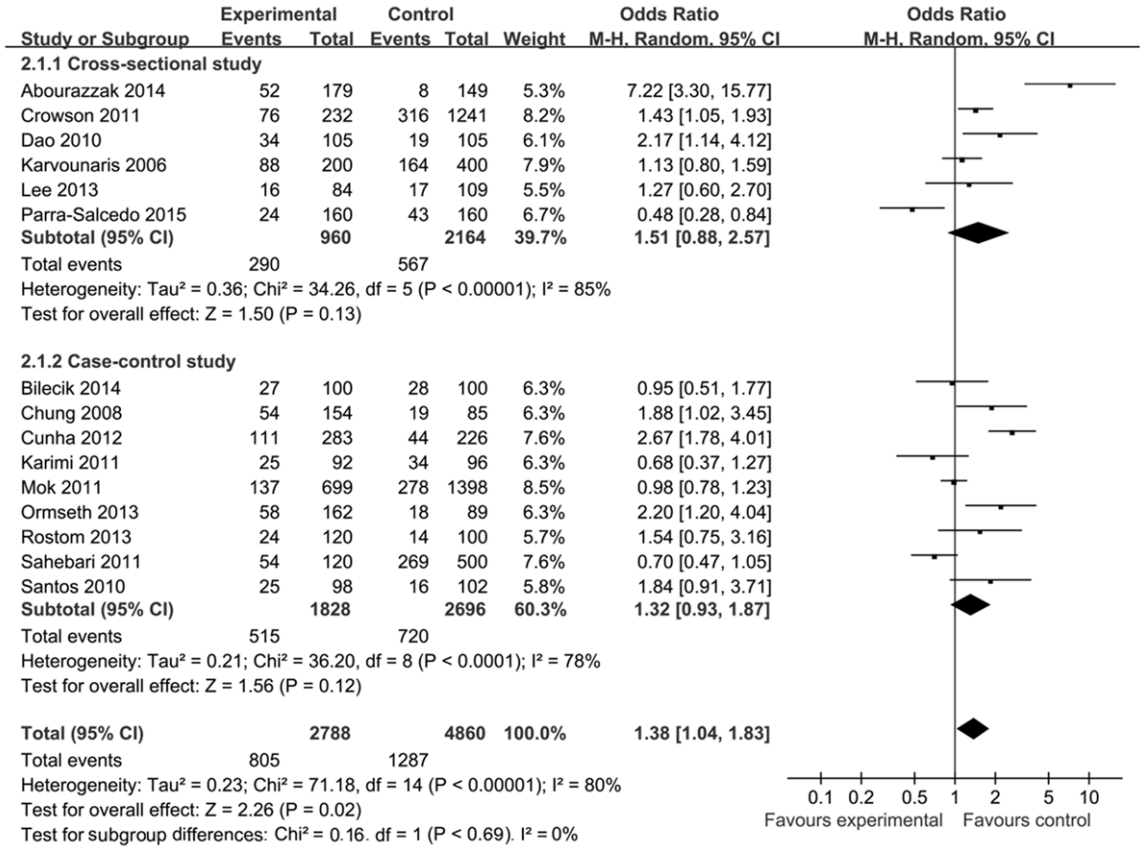

Figure 3. Subgroup analysis of study type.

Discussions

This meta-analysis included 17 articles, involving a total of 8787 participants (3251 RA patients and 5536 healthy individuals). Interestingly, we found that RA patients had a pronounced higher prevalence of MetS than healthy controls, only applying the diagnostic criteria of NCEP-ATP III, instead of using the WHO or IDF criteria.

CVD is considered as the major reason for death in RA patients, and MetS is a clustering of risk factors of CVD [6, 29]. Inflammation is one major hallmark of RA, and accumulating evidence demonstrates that many pro-inflammatory cytokines, such as IL-1, IL6 and TNF-α, are involved in progression of RA [30, 31]. In fact, MetS is associated with subclinical inflammation [32], and metabolic inflammation plays important roles in CVD [33]. Therefore, it is understandable that RA patients achieved a higher incidence of MetS, in comparison with the healthy control. Furthermore, emerging evidence supports the concept that the accumulated adipose tissue macrophage exerts significant function during the process of metabolic inflammation [34, 35]. A study further confirms that alteration of adipokine could contribute to the promotion of obesity-related metabolic disorders and CVD [36]. These suggest adipose tissue might be an important linkage between RA and MetS.

At present, three standards are widely used for diagnosis of MetS, including the WHO, NCEP-ATP III and IDF criteria [37-39]. However, different criteria might generate different results. Reportedly, prevalence of MetS varies depending on different diagnostic criteria, and it is commonly higher based on IDF than NCEP-ATP III [40]. Another study indicates a comparable incidence of MetS using NCEP-ATP III with using IDF criteria among children and adolescents, but a higher prevalence using modified WHO criterion than the other two criteria [38]. Although IDF and NCEP-ATP III are often used for the diagnosis of MetS or for comparison,

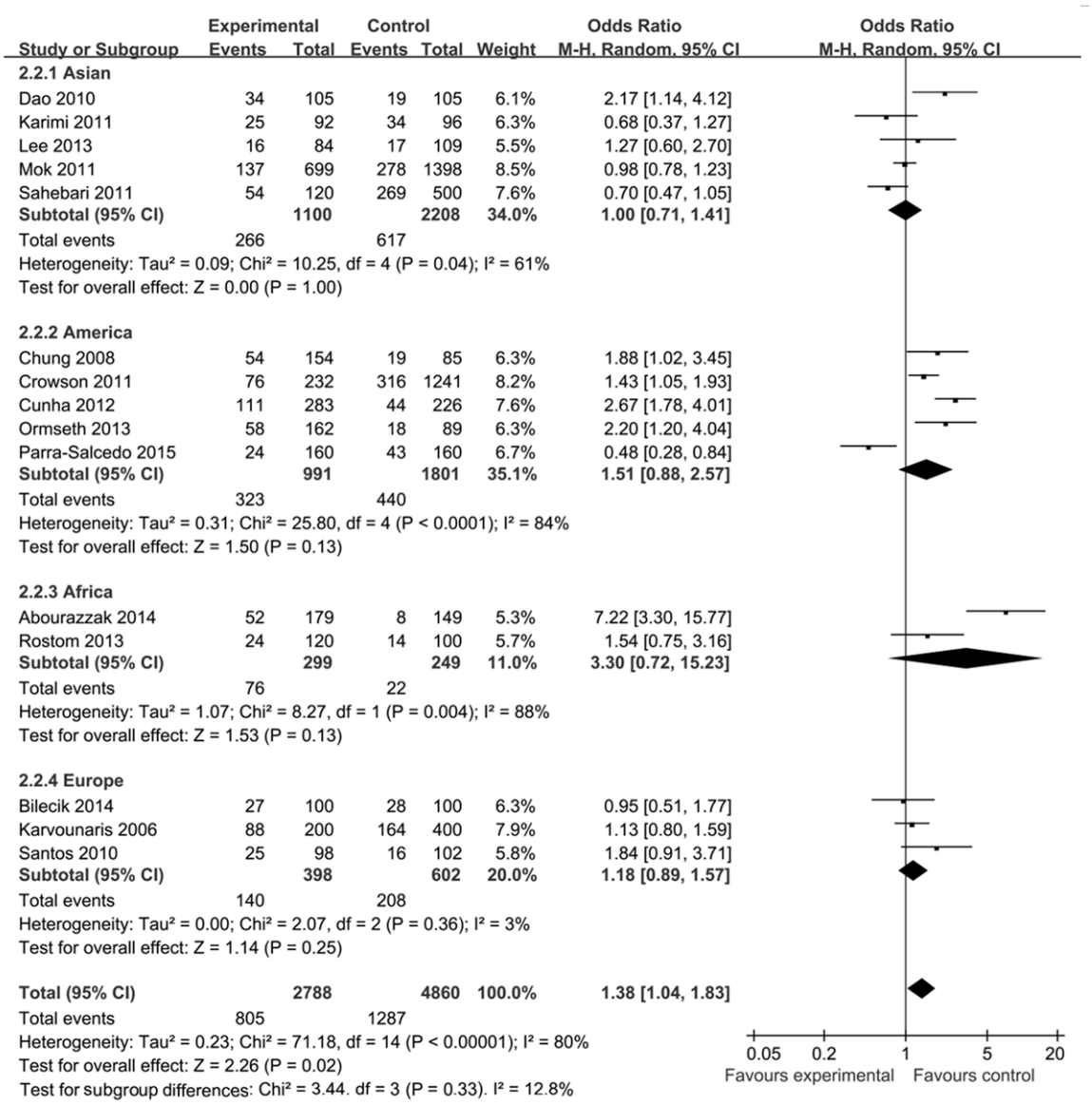

Figure 4. Subgroup analysis of geographic region.

NCEP-ATP III is more frequently used. In our study, a total of 14 studies applied the NCEP-ATP III diagnostic criterion. Based on the previous meta-analysis, RA was associated with the prevalence of MetS, only with the NCEP-ATP III criterion, but not with IDF or WHO criteria [11], which is consisted with our findings. This prompts us that NCEP-ATP III might be more appropriate for MetS diagnosis to investigate its association with RA.

As our results indicated, substantial heterogeneities were presented. To further investigate the potential causative factors, we performed subgroup analysis stratified by region, study type and sex composition for studies using NCEP-ATP III as the diagnostic criterion for MetS. Unexpected, we did not detect any significant difference on MetS prevalence between RA patients and healthy controls, when stratified by region ($P > 0.05$). This might be explained by an almost equal distribution of articles in Asian, America, Europe and Africa. Considering only 2-5 studies were included in each subgroup of geographic regions, we could not conclude whether region is a confounder factor for substantial heterogeneity, but just suggest that more studies in relevant countries are required. Cross-sectional study might be insensitive when determine the directionality between

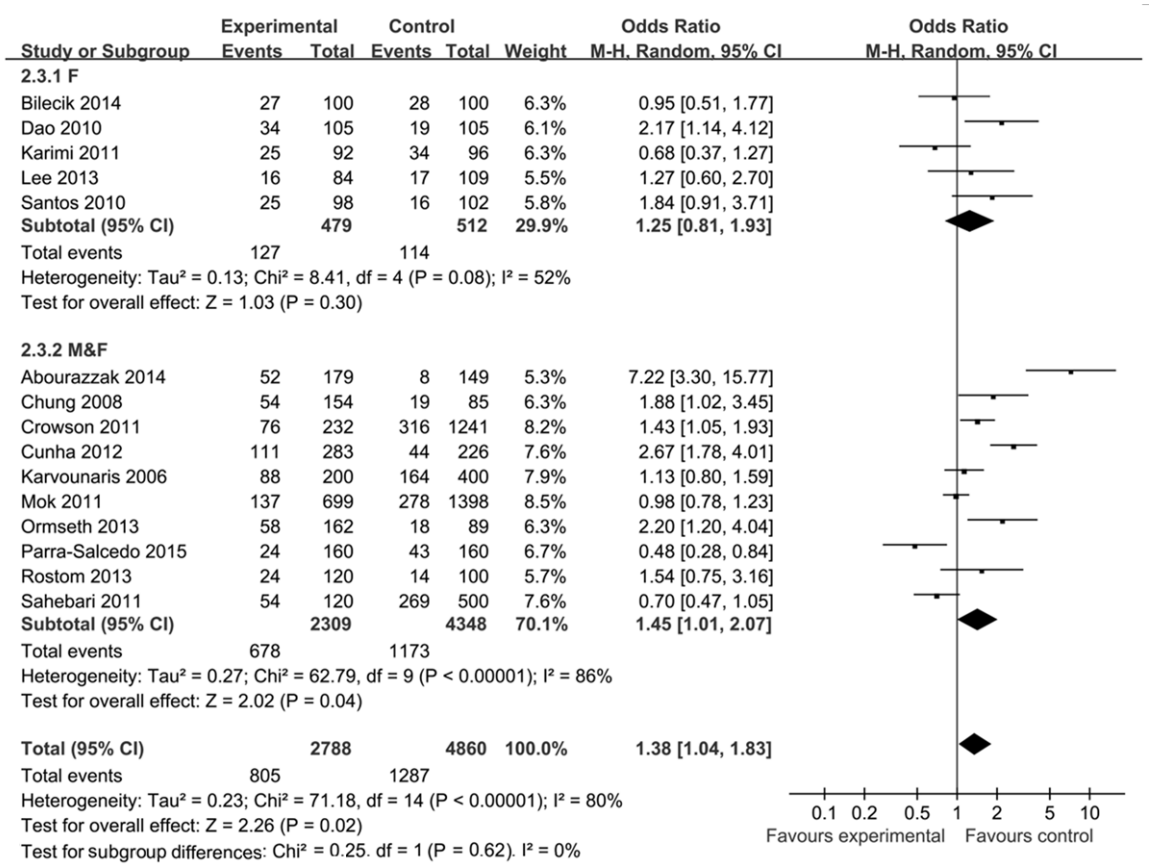

Figure 5. Subgroup analysis of sex composition.

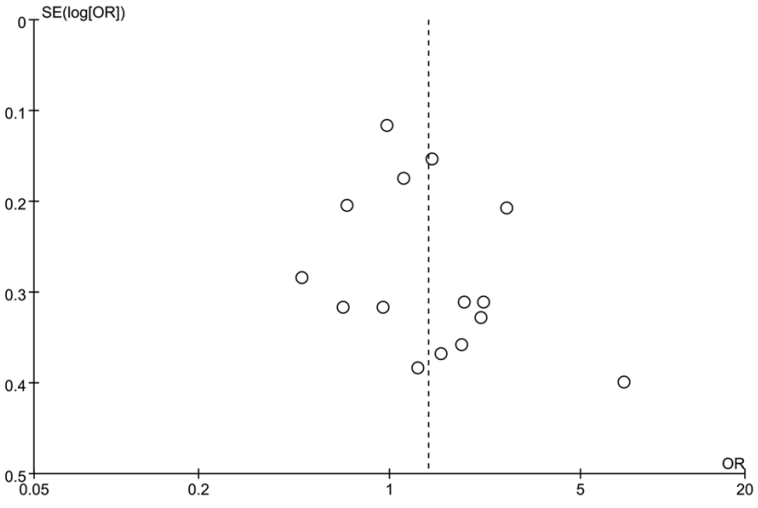

Figure 6. Funnel plot of all the included studies.

MetS and related diseases [41]. Our findings that RA was not associated with prevalence of MetS in neither cross-sectional studies, nor case-control studies, suggesting study type was not a causative factor for heterogeneity. With regard to sex composition, although Zhang's meta-analysis did not consider this factor for subgroup analysis, they implied it might influence the overall result [11]. We did not confirm this hypothesis but found that in female subgroup, RA was not pronouncedly related to the prevalence of MetS ($P > 0.05$). Due to the limited research data, the male subgroup could not be extracted separately, we failed to estimate whether male patients with RA were more likely to develop MetS or not.

Despite the fact that 17 eligible studies were all with larger sample size and high quality, there are several limitations in the meta-analysis. First, all the included studies were observation-

al studies, and there lacked prospective studies. Although several confounding factors were adjusted, the correlation between RA and MetS risk could still be affected by certain unadjusted confounding factors. Second, significant heterogeneity existed across studies, which might cause some bias of the result. Fortunately, we have conducted subgroup analyses to recognize potential resources of heterogeneity. Third, treatment of RA could influence the components of MetS; however, neither of the included studies mentioned the related issue. Thus, we did not take this factor into consideration, which might affect the accuracy of MetS diagnosis. Therefore, more high-quality prospective studies are necessary to verify the result that RA patients had higher prevalence of MetS than healthy individuals.

In conclusion, high prevalence of MetS is significantly associated with RA, especially when using the NCEP-ATP III diagnostic criterion. Prevalence of MetS might be used as an indicator for RA progression. However, more prospective studies with larger sample size are required to confirm these results.

Disclosure of conflict of interest

None.

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