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Review

The association between metabolic syndrome and polycystic ovary syndrome: A systematic review and meta-analysis

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ABSTRACT

Background: One of the most frequently encountered endocrinopathy in women of reproductive age is polycystic ovary syndrome (PCOS). Recent studies have reported varied prevalence of metabolic syndrome (MetS) in women with PCOS. The aim of this study is to determine if the women with PCOS are at a higher risk of MetS.

Method: The present systematic review and meta-analysis was conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. To collect articles, we searched online databases of PubMed/Medline, Scopus, Web of Science, Science Direct, Embase, CINAHL, Cochrane Library, EBSCO and Google scholar search engine and the reference list of the retrieved articles using MeSH keywords of "metabolic syndrome", "woman" and "polycystic ovary syndrome" without time limit until October 2018. Cochran's Q test and I^2 Index were used to evaluate the heterogeneity among studies and the random effects model was used for combining the results. Data analysis was performed in STATA software version 11.1.

Result: Finally, 72 studies involving 10075 PCOS patients with an average age of 26.2 ± 5.01 years were included in the meta-analysis. The heterogeneity rate was high ($I^2 = 76.5\%$; $p < 0.001$) and the pooled estimate of the association between MetS and PCOS was significant (OR = 2.57, 95% CI: 2.18–3.02; $P < 0.001$).

Conclusion: According to the results, there is higher risk of MetS in women with PCOS. Therefore, diagnosis and treatment of MetS in women with PCOS may have a significant impact on this patients health and reduce the rate of mortality and morbidity.

1. Introduction

One of the most frequently encountered endocrinopathy in women of reproductive age is polycystic ovary syndrome (PCOS) that affect about 10% of women [1,2]. This disorder is characterized by hyperandrogenism, and chronic anovulation and polycystic ovaries in sonography [3]. The exact etiology of PCOS is still unknown [4]. Due to insulin resistance, women with PCOS are susceptible to Type II diabetes mellitus and cardiovascular disease [5]. PCOS women are at higher risk of metabolic and endocrine disorders, which are the components of metabolic syndrome such as hyperinsulinemia, hyperglycemia, impaired glucose tolerance, dyslipidemia and obesity [6,7] (see Table 1).

Different studies have suggested that PCOS is associated with MetS, and one of the suggested reasons is that insulin resistance may be an underlying factor and another reason is that obesity and adipocytokines may be related to both of these disorders [8–10]. MetS increases the risk for diabetes and cardiovascular disease [11].

There are different diagnostic criteria for MetS such as COOK, American Heart Association and the National Heart, Lung and Blood Institute (AHA/NHLBI), International Diabetes Foundation (IDF), and The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) [12–15]. Different studies have been conducted to report the MetS prevalence in PCOS patients, which reported different results. Higher prevalence of MetS in obese Greek women with PCOS compared with control group was reported in a study by Kyrkou et al. [16]. The studies of Albu et al., Boyle, and Bhattacharya

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Table 1
Data obtained from Articles on the association between metabolic syndrome and polycystic ovary syndrome.

Author	year	MetS[a] Criteria	Case	Mean age (SD[b])	Mean BMI[c]	MetS-Positive	Control	Mean age (SD)	Mean BMI	MetS-Positive
Dokras [7]	2005	WHO[d]	129	28		61	177	44		8
Hahn [24]	2007	IDF[e]	411	28 (6.3)	31.3 (9.8)	139	82	28 (7.5)	22.8 (3)	6
Santos [25]	2017	ISS[f]	191	22.89 (6.7)	29.7 (6.4)	51	100	25.2 (7.7)	27.04 (6.09)	5
Rossi [26]	2008	IDF	43	15.6 (1.5)	36.6 (6.9)	11	31	14.8 (1.8)	34 (5.2)	6
Rossi [26]	2008	COOK	43	15.6 (1.5)	36.6 (6.9)	23	31	14.8 (1.8)	34 (5.2)	17
Rossi [26]	2008	AHA/NHLBI[g]	43	15.6 (1.5)	36.6 (6.9)	11	31	14.8 (1.8)	34 (5.2)	9
Coviello [27]	2006	NCEP ATPIII[h]	49	17 (2)	32 (9)	18	165	15 (2)	23 (5)	8
Hudecova [28]	2011	NCEP ATPIII	84	43 (5.8)	28.3 (6)	20	87	43.7 (6.2)	25.7 (4.4)	7
Glueck [29]	2003	NCEP ATPIII	138	31 (9)		64	1887			430
Park [30]	2007	NCEP ATPIII	117	26 (5)	23.6 (4.5)	16	505	23.3 (2.9)	46.6 (12.2)	22
Behboudi [31]	2016	JSS	50	33.04 (6.5)	28.69 (6.52)	8	704	36.89 (7.86)	25.2 (4.39)	98
Gambineri [32]	2009	IDF	200	26.1 (5.5)	31.7 (7.4)	78	200	26.8 (6)	31 (7.6)	50
Gambineri [32]	2009	NCEP ATPIII	200	26.1 (5.5)	31.7 (7.4)	64	200	26.8 (6)	31 (7.6)	46
Gambineri [32]	2009	AHA/NHLBI	200	26.1 (5.5)	31.7 (7.4)	74	200	26.8 (6)	31 (7.6)	48
Rahmanpour [33]	2012	IDF	30	17.73 (1.01)	23.4 (3.09)	10	71	17.69 (1.29)	21.06 (2.85)	8
Anjum [34]	2013	NCEP ATPIII	225			80	200			19
Romanowski [35]	2015	NCEP ATPIII	101	26.8 (5)	28.5 (6)	33	30	33.7 (7)	26.1 (4)	8
Romanowski [35]	2015	IDF	101	26.8 (5)	28.5 (6)	45	30	33.7 (7)	26.1 (4)	11
Jamil [36]	2015	NCEP ATPIII	263	26.78 (4.95)	31.08 (5.82)	141	263	29.02 (6.04)	28.66 (5.04)	86
Anaforoglu [37]	2011	NCEP ATPIII	84	23.7 (6.8)	30.1 (8.3)	13	81	24.5 (7.1)	27.2 (6.9)	4
Kyrkou [16]	2016	IDF	230	24.7 (5.7)	26 (7.1)	29	155	24.1 (6.1)	23 (4.3)	3
Albu [17]	2015	NCEP ATPIII	398	24 (7)	26.1 (10.9)	81	126	28 (10)	25.61 (12)	14
Attaoua [38]	2008	NCEP ATPIII	207			75	100	34.1 (1.1)	22.2 (0.4)	4
Vural [39]	2005	WHO	43	21.4 (1.8)	23.4 (4.7)	5	43	20.8 (2.2)	21.5 (3)	0
Vural [39]	2005	NCEP ATPIII	43	21.4 (1.8)	23.4 (4.7)	1	43	20.8 (2.2)	21.5 (3)	0
Vrbíková [40]	2005	NCEP ATPIII	69	25.2 (4.7)	24.3 (4.8)	1	73		22.3 (3.3)	0
Cheung [41]	2008	NCEP ATPIII	295	30.2 (6.4)	25.8 (5.9)	72	98	33.4 (5.9)	21.3 (2.6)	3
Cussons [42]	2008	IDF	168	34.3 (6.3)	32.3 (8.1)	67	883	33.7 (6.5)	25.8 (5.8)	115
Cussons [42]	2008	NCEP ATPIII	168	34.3 (6.3)	32.3 (8.1)	62	883	33.7 (6.5)	25.8 (5.8)	88
Macut [43]	2016	IDF	222	25.01 (4.89)	22.99 (4.57)	41	45	28.58 (4.91)	21.62 (3.88)	3
Macut [43]	2016	NCEP ATPIII	222	25.01 (4.89)	22.99 (4.57)	36	45	28.58 (4.91)	21.62 (3.88)	3
Macut [43]	2016	JIS[i]	222	25.01 (4.89)	22.99 (4.57)	43	45	28.58 (4.91)	21.62 (3.88)	3
Boyle [18]	2015	NCEP ATPIII	35	32	33.4	18	74	33	23.8	17
Bhattacharya [19]	2011	JIS	51	17.06 (1.6)	26.37 (4.6)	31	45	16.69 (1.7	25.38 (4.6)	12
Carmina [44]	2006	NCEP ATPIII	282	24.9 (0.1)	27.2 (0.3)	23	85	25.2 (0.2)	23.3 (0.6)	2
Carmina [44]	2006	IDF	282	24.9 (0.1)	27.2 (0.3)	45	85	25.2 (0.2)	23.3 (0.6)	2
Shroff [45]	2007	NCEP ATPIII	258	(5.3)27	[9]35	92	110	(6.6)37.9	[6]29	13
Faloia [46]	2004	NCEP ATPIII	50	22		10	20	26	27 (9)	3
Blasco [47]	2006	NCEP ATPIII	32	26 (7)	34.8 (6.6)	8	72	32 (8)	35.2 (6.2)	19
Welt [48]	2006	Unknown	418	29.6 (6)	27 (6.8)	74	64	30.8 (6.1)	27.3 (6.8)	7
Caliskan [49]	2007	NCEP ATPIII	182	23.21 (4.5)	25.04 (5.1)	15	182	23.6 (4.6)	23.52 (2.9)	5
Caliskan [49]	2007	IDF	182	23.21 (4.5)	25.04 (5.1)	26	182	23.6 (4.6)	23.52 (2.9)	5
Caliskan [49]	2007	WHO	182	23.21 (4.5)	25.04 (5.1)	15	182	23.6 (4.6)	23.52 (2.9)	5
Caliskan [49]	2007	AHA/NHLBI	182	23.21 (4.5)	25.04 (5.1)	19	182	23.6 (4.6)	23.52 (2.9)	12
Caliskan [49]	2007	Rotterdam	182	23.21 (4.5)	25.04 (5.1)	18	182	23.6 (4.6)	23.52 (2.9)	5
Gulcelik [50]	2008	NCEP ATPIII	60	24.6 (4.6)	28 (5.5)	20	60	26.1 (4.9)	26.7 (4.5)	7
Shaw [51]	2008	ATPIII	104	62.5 (10)	31.1	58	286	65.8 (9)	28.4	125
Roe [52]	2013	COOK	148	16.9 (1.9)	28.5 (7.4)	16	57	16.6 (2.5)	24.7 (7.1)	1
Rehme [53]	2013	NCEP ATPIII	60	28.9 (5.3)	37.4 (5.5)	45	70	27.4 (5.2)	36 (4.3)	37
Pau [54]	2013	NCEP ATPIII	111	27.4 (0.6)	30.9 (0.8)	16	58	27.6 (0.8)	25.8 (0.8)	2
Sharma [55]	2015	NCEP ATPIII	120	29.8 (4.2)	27.38 (5.9)	47	80	30.61 (4.01)	24.62 (5.06)	19
Bozic-Antic [56]	2016	NCEP ATPIII	365	25.48 (5.21)	25.05 (6.24)	73	125	30.35 (5.62)	25.41 (5.16)	6
Bozic-Antic [56]	2016	IDF	365	25.48 (5.21)	25.05 (6.24)	84	125	30.35 (5.62)	25.41 (5.16)	14
Bozic-Antic [56]	2016	JIS	365	25.48 (5.21)	25.05 (6.24)	86	125	30.35 (5.62)	25.41 (5.16)	15
Amato [57]	2008	IDF	104	23.8 (5.38)	30.66 (6.69)	28	100	25.47 (6.16)	29.83 (7.2)	15
Amato [57]	2008	IDF	170	24.47 (5.79)	30.49 (6.95)	37	34	25.35 (5.98)	29.09 (6.88)	6
Amato [57]	2008	IDF	144	24.06 (5.4)	30.43 (6.8)	34	60	25.97 (6.57)	29.83 (7.32)	9
Hosseinpanah [20]	2011	JIS	136	31 (7.7)	26.4 (5.8)	25	423	36 (7.5)	26.4 (5)	78
Lankarani [58]	2009	NCEP ATPIII	55	23.75 (5.26)	24.93 (5.32)	7	59	24.49 (5.4)	21.56 (2.56)	1
Liang [59]	2012	NCEP ATPIII	220	26.9 (5.8)	25.9 (6.1)	66	70	28.3 (4.4)	23.4 (5.2)	10
Melo [60]	2011	NCEP ATPIII	226	26.6 (5.1)	28.9 (0.5)	86	146	28.9 (0.5)	24.4 (4.9)	12
Nandalike [61]	2012	IDF,JSS	28	16.8 (1.9)	44.8 (8.8)	10	28	17.1 (1.8)	40.2 (4.7)	4
Panidis [62]	2013	NCEP ATPIII	1223	24.7 (5.8)	27.5 (6.9)	193	277	31.3 (5.4)	26.6 (6.7)	28
Panidis [62]	2013	AHA/NHLBI	1223	24.7 (5.8)	27.5 (6.9)	292	277	31.3 (5.4)	26.6 (6.7)	52
Panidis [62]	2013	IDF	1223	24.7 (5.8)	27.5 (6.9)	353	277	31.3 (5.4)	26.6 (6.7)	66
Panidis [62]	2013	JIS	1223	24.7 (5.8)	27.5 (6.9)	360	277	31.3 (5.4)	26.6 (6.7)	66
Panidis [62]	2013	NCEP ATPIII	1223	18.1 (1.7)	27.8 (7)	191	277	18.3 (1.1)	21.3 (2.2)	36
Panidis [62]	2013	AHA/NHLBI	1223	18.1 (1.7)	27.8 (7)	290	277	18.3 (1.1)	21.3 (2.2)	52
Panidis [62]	2013	IDF	1223	18.1 (1.7)	27.8 (7)	350	277	18.3 (1.1)	21.3 (2.2)	66
Panidis [62]	2013	JIS	1223	18.1 (1.7)	27.8 (7)	360	277	18.3 (1.1)	21.3 (2.2)	66
Tehrani [63]	2014	JIS	85	29.07 (7.7)		6	517	33.9 (7.6)	26.6 (5)	101

Table 1 (*continued*)

Author	year	MetS[a] Criteria	Case	Mean age (SD[b])	Mean BMI[c]	MetS-Positive	Control	Mean age (SD)	Mean BMI	MetS-Positive
Vrbíková [64]	2011	IDF	43	16.84 (1.97)	23.64 (6.1)	5	48	17.5 (1.85)	23.3 (5.2)	1
Wijeyaratne [65]	2011	NCEP ATPIII	395	25 (9)	24.9 (6.43)	121	205	29		13

[a] Metabolic syndrome.
[b] Standard deviation.
[c] Body Mass Index.
[d] WHO: World health organization.
[e] IDF: International diabetes foundation.
[f] JSS: Joint scientific statement.
[g] AHA/NHLB: American Heart Association and the National Heart, Lung and Blood Institute.
[h] NCEP ATPIII: The national cholesterol education program adult Treatment Panel.
[i] JIS: Joint interim statement.

also demonstrated higher prevalence of MetS in PCOS women compared with control group [17–19]. In a study by Hosseinpanah et al., there was no difference in the prevalence of MetS in women with PCOS and the healthy control group based on JIS criteria (18.5% in the case group and 18.3% in the control group) [20]. The present systematic review and meta-analysis was performed to review all the relevant documents to find the association between MetS and PCOS.

2. Method

2.1. Study protocol

The present systematic review and meta-analysis was reported using the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines to determine the association between MetS and PCOS [21]. All steps of the study were independently performed by two researchers and any disagreement between researchers was resolved by a third researcher .

2.2. Search strategy

We searched the online databases of PubMed/Medline, Scopus, Web of Science, Science Direct, Embase, CINAHL, EBSCO and Google scholar search engine using MeSH keywords of “metabolic syndrome”, “prevalence”, “woman” and “polycystic ovary syndrome” without time limit until October 2018. All the reference lists of the retrieved articles were reviewed.

2.3. Inclusion and exclusion criteria

Inclusion criteria were studies addressing the association between MetS and PCOS with at least an English abstract. The exclusion criteria were as follows: 1. No PCOS or MetS as the outcome; 2. Review articles, conference presentations, and letters to the editor; and 3. Low quality studies.

2.4. Quality assessment

In the next step, the selected articles were reviewed using the modified Scale of Newcastle Ottawa (NOS) for non-randomized studies [22]. In the checklist, the lowest acceptable score was considered 4 and the studies that reached this score were included in the study.

2.5. Criteria for metabolic syndrome

IDF, Joint Scientific Statement (JSS), COOK, NCEP ATP III, American Heart Association AHA/NHLBI, World Health Organization (WHO), and Joint Interim Statement (JIS).

2.6. Data extraction

In the next step , the following data were extracted for each study: author(s) name, country, study design, year of study, MetS criteria, name of journal, samples characteristics for patients and controls (e.g. mean age and SD [Standard Deviation], and BMI [Body Mass Index] and SD), diagnostic criteria, odds ratio (OR), 95% confidence interval (CI), number of MetS positive in case and control groups.

2.7. Statistical analysis

Cochran's Q test and I^2 Index were used to evaluate the heterogeneity among studies (The I^2 indexes of lower than 25%, 25-75%, and higher than 75% were considered as low, moderate and high heterogeneity, respectively) [23]. Considering the high heterogeneity, the random effects model was used for combining the result of different studies. Sensitivity analysis by excluding one study at a time was performed to evaluate the strength of combined OR and 95% CI. Subgroup analysis based on PCOS criteria was performed to find the source of heterogeneity. Egger and Begg's test was used to evaluate publication bias and was presented in funnel plot. We also conducted cumulative analysis based on the year of publication. Data analysis was performed in STATA software version 11.1. Data were presented through flowcharts, summary tables, OR and funnel plots. The significance level was considered as 0.05.

3. Results

3.1. Search results and characteristics of the articles

In the initial search, 560 articles were collected, and 280 duplicate articles were detected and excluded by EndNote software. The title and abstract of articles were reviewed and 131 irrelevant articles were excluded. Then, after studying the full text of articles, 72 articles conducted on 10,075 PCOS cases were included in the final analysis (6 articles were excluded in quality assessment) (Fig. 1).

3.2. The association between MetS and PCOS

The heterogeneity rate was high ($I^2 = 76.5\%$; $p < 0.001$) and the overall pooled estimate of the association between MetS and PCOS was significant (OR = 2.57, 95% CI: 2.18–3.02; $p < 0.001$) (Fig. 2). The cumulative analysis based on the publication year is shown in Fig. 3.

3.3. Sensitivity analysis

Sensitivity analysis was conducted by analyzing the data after

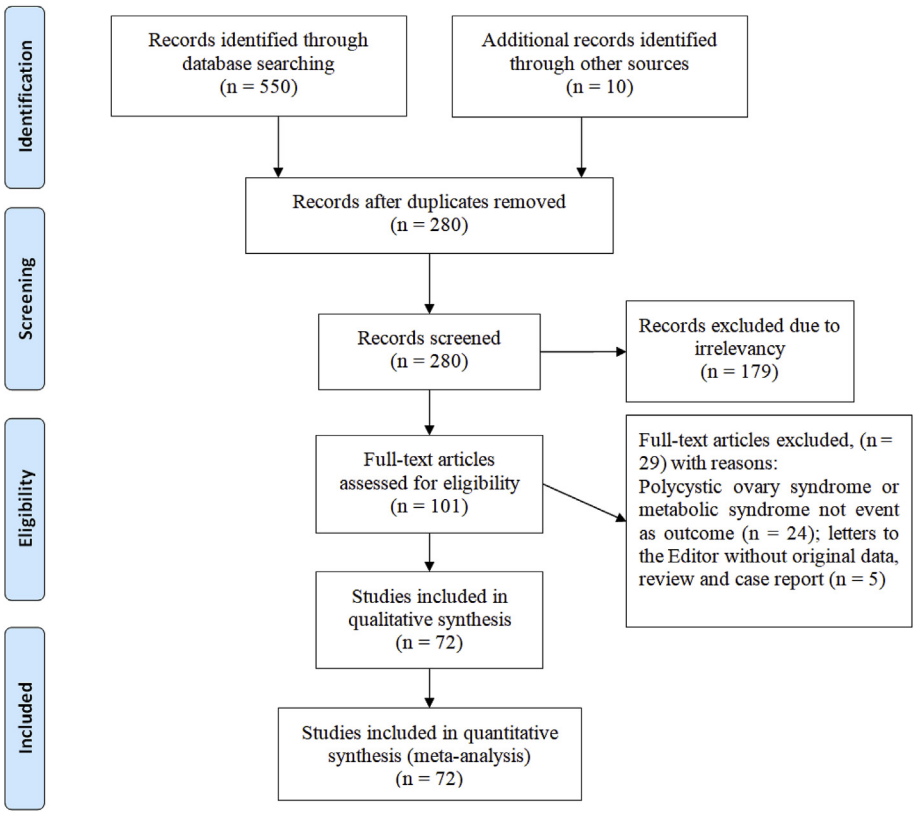

Fig. 1. PRISMA flowchart.

removing two studies, the pooled result was strong.

3.4. Sub group analysis

Analysis of studies based on the method used to identify PCOS indicated an OR of 2.41 (95% CI: 1.75–3.31), 2.80 (95% CI: 0.47–16.58), 2.08 (95% CI: 0.29–14.99), 3.13 (95% CI: 2.51–3.90), 1.44 (95% CI: 1.18–1.74), 8.10 (95% CI: 2.51–26.11) and 1.43 (95% CI: 0.95–2.15) for IDF, JSS, COOK, NECP-ATPIII, AHA/NHLBI, WHO, JIS criteria, respectively (Table 2).

3.5. Meta-regression

In meta-regressionanalysis, p-values for age were 0.015 and 0.018 respectively in cases and controls but for BMI were 0.73 and 0.2 respectively in cases and controls.

3.6. Publication bias

Based on Egger's test, p-value for publication bias of the association between MetS and PCOS was estimated 0.001 (Fig. 4).

4. Discussion

After searching the related databases, 72 studies were finally included in the final analysis and the overall OR of the association between MetS and PCOS was estimated 2.57 (95% CI: 2.18-3.02; P<0.001), indicating the higher risk of MetS in women with PCOS compared to non-PCOS women. Rate of heterogeneity in our study was high (I^2 =76.5%; p=0.000), which may be due to different diagnostic criteria for MetS; therefore, subgroup analysis based on diagnostic criteria was performed.

In meta-regression analysis, the effect of age in cases and controls on heterogeneity was significant but the effect of BMI on heterogeneity was not significant. It is possible that another unknown factor be the source of heterogeneity in this study.

Egger's test p-value and funnel plot shows a significant effect for publication bias, suggesting that some articles with significant effect may not have been published.

Based on sensitivity analysis, the effect of each article on OR was examined after removing two studies, and the result was significant.

The present study supports the results of a meta-analysis by Moran et al. on MetS. Their study analyzed 16 articles, including 2256 cases with PCOS and 4130 controls without PCOS, and higher prevalence of MetS, IGT and DM2 was reported in PCOS patients and the OR for the association with MetS was 2.88 (95% CI: 2.40–3.45) [66].

The study of Aydin et al. recommended determining MetS even in normal BMI girls [67]. However, studies of Panidis et al. and Rahmanpour et al. reported that the prevalence of MetS in PCOS patients was higher in obese women, while rahmanpour suggested that PCOS and obesity are two independent risk factor for MetS in adolescent (62,33). Study of Liang et al. showed the obesity more than hyperandrogenism, chronic anovulation and polycystic ovary morphology increases the risk of MetS and glucose intolerance in women with PCOS and suggested that obesity should be treated in these women [59].

The study of Behboudi-Gandevani et al. suggested waist to height ratio as a good predictor of insulin resistance and MetS in healthy and PCOS women [31].

In the study by Ziaee et al., higher rate of MetS and

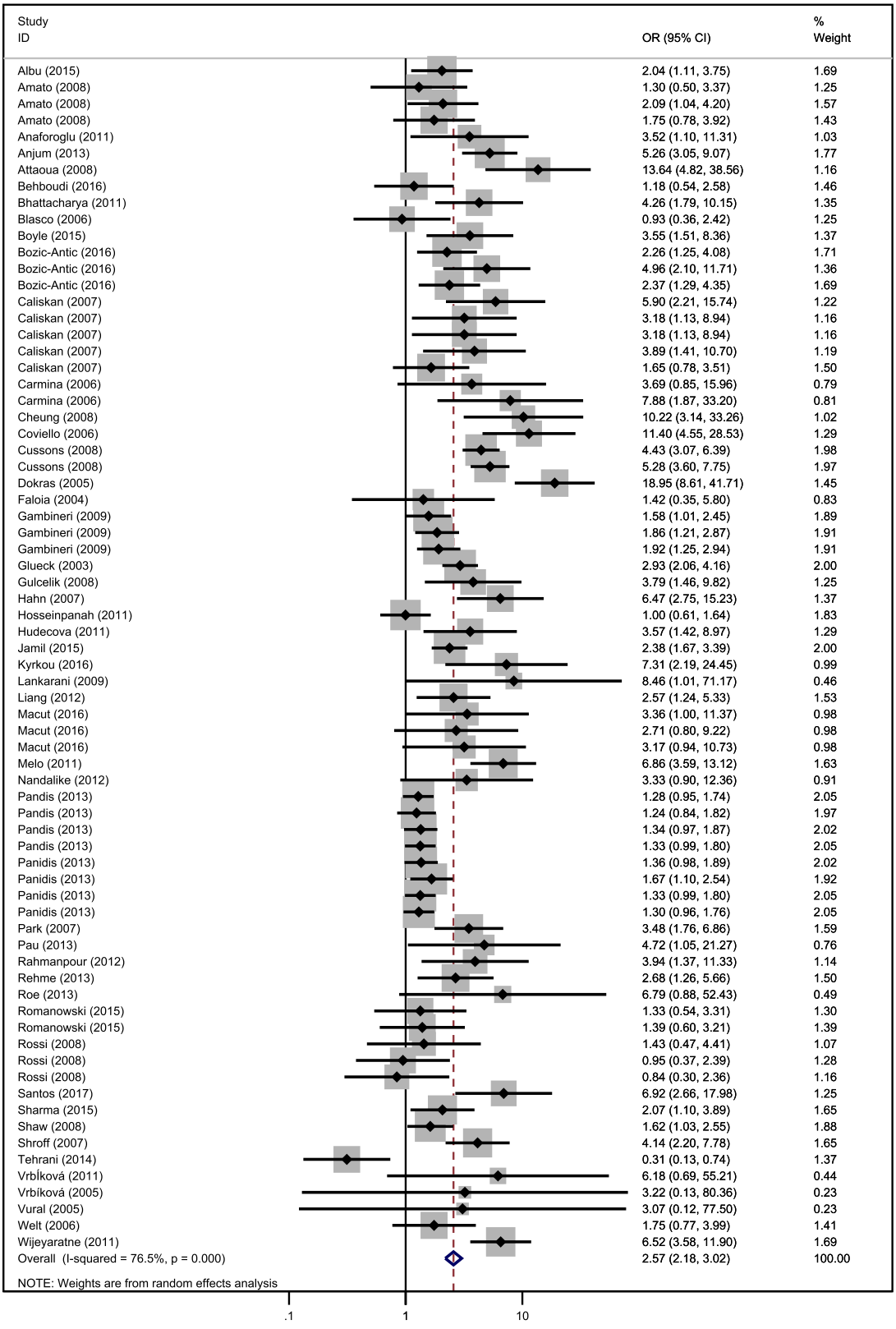

Fig. 2. Meta-analysis of studies on association between metabolic syndrome and polycystic ovary syndrome (mean point of each segment shows the estimated odds ratio (OR), and the length of each segment shows 95% confidence interval (CI) in each study; the diamond mark shows the OR in each study).

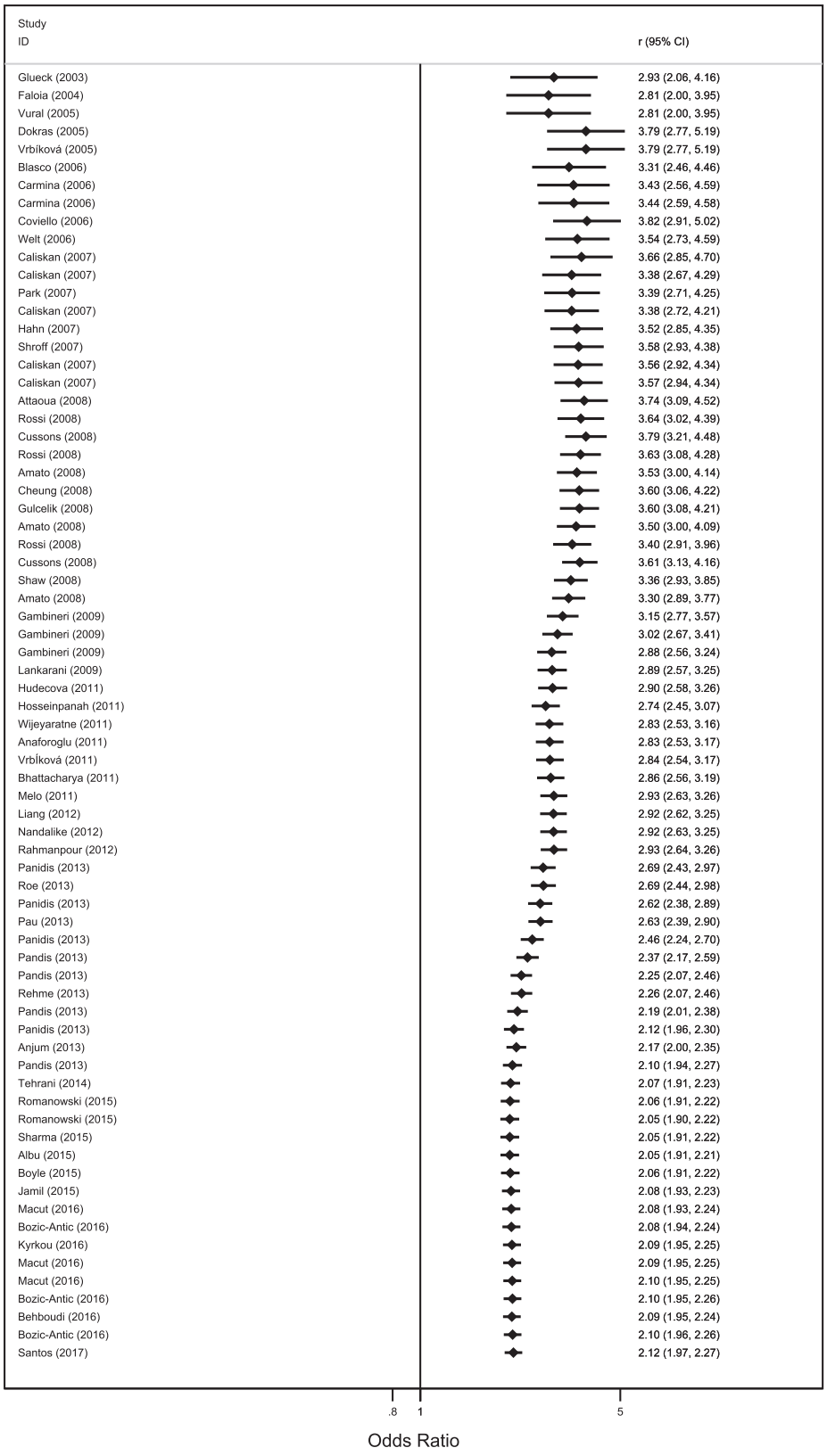

Fig. 3. Cumulative analysis of studies on the association between metabolic syndrome and polycystic ovary syndrome.

Table 2
Meta-analysis of studies on the association between metabolic syndrome and polycystic ovary syndrome according to metabolic syndrome diagnostic criteria.

Diagnostic criteria	IDF[a]	JSS[b]	COOK	NECP-ATPIII[c]	AHA/NHLBI[d]	WHO[e]	JIS[f]
Studies (n)	16	2	2	34	5	3	7
OR[g]	2.41	2.80	2.08	3.13	1.44	8.10	1.43
95%CI[h]	1.75–3.31	0.47–16.58	0.29–14.99	2.51–3.90	1.18–1.74	2.51–26.11	0.95–2.15
I[b]	73.3%	87.9%	69.1%	69.1%	0%	72.7%	75.5%

[a] IDF: International diabetes foundation.
[b] JSS: Joint scientific statement.
[c] NCEP ATPIII: The national cholesterol education program adult Treatment Panel.
[d] AHA/NHLB: American Heart Association and the National Heart, Lung and Blood Institute.
[e] WHO: World health organization.
[f] JIS: Joint interim statement.
[g] OR: Odds ratio.
[h] Confidence interval.

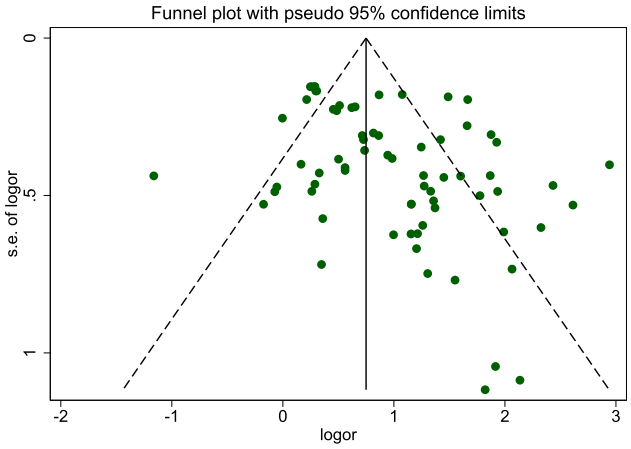

Fig. 4. Publication bias in meta-analysis of studies on association between metabolic syndrome and polycystic ovary syndrome.

premicroalbuminuria was reported in patients with PCOS compared to normal controls, and reported that microalbuminuria may play a role as a risk factor for cardiovascular disease [68,69].

5. Conclusion

Our findings indicate that women with PCOS are at a higher risk of MS and its consequences, so it is important to aware women with PCOS of the risk of MS and cardiovascular disease and other complication of this disorder and there is need for screening for MetS in women with PCOS and need for health care programs and management such as diet and exercise programs.

Conflicts of interest

There is no conflict of interest at all.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.01.002.

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