
1 **Meta-Analysis**

2 **Title: Circulating adipokines in non-obese PCOS patients: a
3 systematic review and meta-analysis**

4 **Running title: adipokines in non-obese PCOS**

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18 **Key Words:** polycystic ovary syndrome; adipokine; non-obese; systematic review;
19 meta-analysis

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
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43 **Abstract**

44 Concentrations of circulating adipokines in non-obese polycystic ovary syndrome
45 (PCOS) patients had been reported in many researches, however, these results were
46 conflicting. The aim of this meta-analysis was to assess whether the levels of
47 circulating adipokines were changed in non-obese PCOS. To identify eligible studies,
48 literature research was performed in the database of PubMed, Embase, Web of
49 Science without the restriction of region, publication or language. Of the total studies
50 found, only 81 met the inclusion criteria. The meta-analysis showed that circulating
51 levels of adiponectin [-0.95 (95% CI, -1.36 to -0.53)] decreased statistically in
52 non-obese PCOS women. On the contrary, circulating levels of chemerin [1.13 (95%
53 CI, 0.08 to 2.18)], leptin [0.47 (95% CI, 0.13 to 0.81)], resistin [0.45 (95% CI, 0.03 to
54 0.88)] and visfatin [1.38 (95% CI, 0.68 to 2.09)] increased significantly in non-obese
55 PCOS females. Besides, there was no statistically significant change in the circulating
56 levels of apelin [0.32 (95% CI, -1.34 to 1.99), irisin [1.01(95% CI, -0.68 to 2.70),
57 omentin [-0.37(95% CI, -1.05 to 0.31)] and vaspin [0.09(95% CI, -0.14 to 0.32)] in
58 non-obese PCOS patients. Scientific evidence suggested that the levels of circulating
59 adipokines altered in non-obese PCOS patients compared with controls. Independent
60 of the degree of obesity, the abnormal change of circulating adipokines levels might
61 play an important role in the occurrence and development of PCOS.

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74 1.Introduction

75 PCOS is a common endocrine and metabolic disease ,which affects nearly affects
76 6%-10% of reproductive-aged women according different criteria¹. PCOS is
77 diagnosed by sparse ovulation or anovulation, hyperandrogenism or/and polycystic
78 ovaries². Current studies have proved that the obesity rate of PCOS patients is
79 significantly increased, which suggests that obesity may be related to the occurrence
80 and symptoms of PCOS³.

81 Fat tissue, which we often think of as a storage site for energy, is a crucial
82 endocrine tissue in the body⁴. Adipokine is an active hormone and factor secreted by
83 adipocytes, including adiponectin, leptin, omentin, etc. These hormones and factors
84 secreted by adipose tissue are involved in many critical physiological processes in the
85 body. Therefore, abnormal changes in adipokines may also lead to some endocrine
86 diseases in the body⁵. Besides, studies have shown that adipokines play an essential
87 role in the pathogenesis of obesity and obesity-related diseases⁶.

88 PCOS patients are likely to have metabolic complications such as type 2 diabetes,
89 IR (insulin resistance), and adipose tissue dysfunction ⁷⁻⁹. While IR affects about 10%
90 to 25% of the general population, compared with two to three times the risk in PCOS
91 patients ^{10, 11}. The incidence of obesity is increased in patients with PCOS [RR (95 CI):
92 2.77 (1.88, 4.10)] compared with patients without PCOS¹². And the symptoms in
93 PCOS patients who combined with obesity aggravates significantly. However, up to
94 now, the mechanism of PCOS has not been determined.

95 Dysfunction of adipose tissue can lead to changes in adipokine levels¹³. Many
96 studies have proved that there are changes in adipokines levels in obese PCOS
97 patients, indicating that adipokines play a role in obese PCOS patients^{14, 15}. But so far,
98 studies on adipokines levels in non-obese PCOS patients have been inconsistent.
99 Moreover, it is not known whether the changes of adipokines are related to PCOS
100 directly or obesity or both. Thus, we aimed to perform this systematic review and
101 meta- analysis to evaluate the levels of different kinds of adipokines in non-obese
102 PCOS women.

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111 **2. Materials and Methods**

112 **2.1. Search Strategy**

113 This systematic review and meta-analysis were designed according to the
114 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
115 statement¹⁶ and Meta-analysis Of Observational Studies in Epidemiology
116 (MOOSE)¹⁷.

117 **2.2. Eligibility Criteria**

118 Studies defining PCOS conforming to the Rotterdam Criteria or other compatible
119 criteria were included. (2) Studies designed about obese women with PCOS were
120 excluded from the study. (3) Reviews, non-human studies and conference
121 proceedings were excluded. (4) Studies without control groups were also excluded. (5)

122 Studies without extractable data(not provided as mean±SD) were excluded.

123 **2.3. Information Sources**

124 To identify eligible studies, exhaustive literature was performed in the
125 electronic database of PubMed, Embase, Web of Science without the restriction of
126 region, publication or language. All articles published before July 2019 was
127 considered for eligibility.

128 **2.4. Search Terms**

129 The search strategy involved the identification of all possible studies using
130 combinations of the following keywords:(“adiponectin,” or “apM-1 Protein,” or
131 “ACRP30 Protein,” ; “ apelin,” ; “ chemerin,” or “TIG2 protein,” ; “ irisin,” or
132 “FRCP2 protein,” ; “ leptin,” or “Obese Protein,” ; “omentin,” or “intelectin 1,” ;
133 “resistin,” ; “vaspin,” or “SERPINA12 protein,”; “visfatin,” or “NAMPT Protein,”)
134 and (“Polycystic Ovary Syndrome,” “PCOS,”). Data on the levels of adiponectin,
135 apelin, chemerin, irisin, leptin, omentin, resistin, vaspin, visfatin was extracted.

136 **2.5. Data Extraction**

137 Two reviewers reviewed all the literature searched and determined whether they
138 met the inclusion criteria independently. Discrepant opinions between the two
139 reviewers were resolved by discussion and consultation with a third reviewer, if
140 necessary. The following information will be obtained from the literature: General
141 study characteristics (name of the first author, year of publication, study location),
142 Age and BMI (body mass index) of participants and summary of conclusions of the
143 study. We used the available data for our analysis.

144 **2.6. Quality Assessment**

145 We used Cochrane Collaboration’s tool to assess the quality of studies
146 included. Seven domains were evaluated by this tool, including random
147 sequence generation, allocation concealment, blinding of participants and
148 personnel, outcome assessment, incomplete outcome data, selective reporting,
149 and other biases. Each indicator has three levels: high risk, low risk and
150 unknown risk. Each indicator was evaluated separately by two reviewers and
151 the differences encountered in the process were unified by discussion. The
152 possibility of publication bias was assessed by visual inspection of the funnel

153 plot and egger's test.

154 **2.7. Statistical Analysis**

155 The software of Review Manager Version 5.3 was used to perform the
156 effects by meta-analysis and to construct forest plot. The expected outcome of
157 each study was a difference in average adipokines levels between PCOS
158 patients and healthy controls. Due to the different measurement methods for
159 each study, Review Manager was used to calculate the standard mean
160 difference (SMD) with 95% confidence intervals. The Cochran's
161 chi-square-based Q statistic test and the I² test were calculated to assess
162 potential heterogeneity between the individual studies. According to
163 significant heterogeneity, moderate heterogeneity and low heterogeneity, we
164 selected a random effect model and a fixed effect model respectively.
165 STATA15.0 version was used for egger's test to check publication bias and
166 trim-and-fill method. The t value was used to determine whether there was
167 publication bias. When t value ≥ 0.05 , it was considered that there might be no
168 publication bias.

169 **3.Result**

170 **3.1. Study Selection**

171 Our search strategy identified 1540 potential articles. One thousand two hundred
172 fifty-six studies were excluded after screening based on title or abstract, and 284
173 potentially relevant studies were assessed by reviewing the full-text article. Among
174 these studies, 203 articles were excluded from the meta-analysis and systematic
175 review owing to lack of control groups or obese subjects. Since data in some articles
176 did not present as Mean \pm SD, we continued to exclude 10 articles. Finally, 71 studies
177 including 2495 subjects with PCOS and 2520 controls met our inclusion criteria for
178 the meta-analysis. Figure 1 presents the search strategy for study selection.

179 **3.2. Characteristics of Included Studies**

180 The features of the included literature were presented in Table1. Among the 81
181 included studies, there are several diagnostic criteria for PCOS: The Rotterdam
182 Criteria were adopted in fifty-three articles; The ESHRE/ASRM consensus had been
183 used in three articles; Nine of the articles used the NIH Criteria; Two article used the
184 Criteria of National Institute of Child Health and Human Disease; Other articles
185 adopted some of the specific standards mentioned in the article. The included studies
186 covered twenty-six countries :There were eight articles from China; Two from Saudi
187 Arabia; nineteen studies from Turkey; One study from Croatia; One article from
188 Netherlands; one article from Pakistan; One article from Denmark; Three articles
189 from India; Four studies from Iran; Three studies from South Korea; Three articles
190 from Taiwan; One studies were based in France; One article was based in the United
191 States; Four articles were based on research in Egypt; seven articles on Greece; Four
192 articles from Italy; one article from Israel; one article from Indonesia; Eight articles
193 were written in Poland; one article from Iraq; In addition to one article in Germany;
194 Brazil contributed two articles; an article from Japan; one article from Australia;
195 eventually there were one articles from Spain and one article from Qatar. The subjects
196 included in the study ranged in age from youth to old age. One criterion for obesity

197 was BMI greater than or equal to 30.0, so the studies we included had a BMI lower
198 than 30.0. The Table1 also briefly listed the primary conclusions of each article.

199 **3.3. The relationship between different kinds of adipokines levels and PCOS**

200 Thirty studies reported the level of adiponectin in non-obese PCOS women as
201 illustrated in Figure 2A which showed the forest plot of those studies; there was
202 significant heterogeneity among studies ($I^2 = 95\%$, $p < 0.00001$). Overall,
203 PCOS was associated with a change in adiponectin level of -0.95 (95% CI, -1.36 to
204 -0.53 ; $P < 0.00001$; $n = 30$ studies, 2565 participants).

205 The four trials ($n = 254$ participants) focused on levels of apelin in non-obese
206 PCOS patients. However, no significant difference was noted between PCOS and
207 circulating apelin [0.32 (95% CI, -1.34 to 1.99 ; $P = 0.70$]. The forest plot of those
208 studies was shown in Figure 2B.

209 Five individual studies were included to compare the levels of chemerin between
210 PCOS and controls. The meta-analysis showed an increased level of 1.13 (95% CI =
211 0.08 to 2.18 ; $P = 0.03$; Figure 2C). There was significant heterogeneity among these
212 studies ($I^2 = 96\%$).

213 Four studies reported the level of irisin in non-obese PCOS patients as illustrated
214 in Figure 2D which showed the forest plot of those studies; there was significant
215 heterogeneity among studies ($I^2 = 97\%$, $P < 0.00001$). Overall, PCOS show no
216 correlation with circulating irisin levels of 1.01 (95% CI, -0.68 to 2.70 ; $P = 0.24$; $n =$
217 4 studies, 282 participants).

218 The twenty-five trials ($n = 2148$ participants) focusing on levels of leptin in
219 non-obese PCOS patients found a statistically increase level of 0.47 (95% CI, 0.13 to
220 0.81 ; $P = 0.007$). The forest plot of those studies was showed in Figure 3A.

221 Five individual studies were included to compare the levels of omentin between
222 non-obese PCOS patients and controls. The meta-analysis showed the equal level of
223 omentin [-0.37 (95% CI = -1.05 to 0.31 ; $P = 0.29$; Figure 3B)]. There was significant
224 heterogeneity among these studies ($I^2 = 89\%$).

225 Eighteen studies reported the level of resistin in non-obese PCOS women as
226 illustrated in Figure 3C which showed the forest plot of those studies; there was
227 significant heterogeneity among studies ($I^2 = 91\%$, $P < 0.00001$). Overall,
228 PCOS was associated with an increase in resistin level of 0.45 (95% CI, 0.03 to 0.88 ;
229 $P = 0.03$; $n = 28$ studies, 1223 participants).

230 The three trials ($n = 348$ participants) focusing on levels of vaspin in patients with
231 PCOS found a nonsignificant change level of 0.09 (95% CI, -0.14 to 0.32 ; $P = 0.43$).
232 The forest plots of those studies were showed in Figure 4A.

233 Twenty-six individual studies were included to compare the level of visfatin
234 between PCOS group and controls. The meta-analysis showed an increased level of
235 1.38 (95% CI = 0.68 - 2.09 ; $P = 0.0001$; Figure 4B). There was significant
236 heterogeneity among these studies ($I^2 = 96\%$).

237 **3.4. Publication Bias**

238 Funnel plot method was used to detect publication bias and Egger's test was used
239 to quantify publication bias. The shape of the funnel plot did not reveal any obvious
240 asymmetry in adiponectin, resistin. However, it seemed that the funnel plot of leptin

241 and visfatin showed publication bias observably (Figure5A.5B.5C.5D). Egger's test
242 was used to provide statistical evidence of funnel plot symmetry. The results still did
243 not suggest any evidence of publication bias in adiponectin and leptin. Egger's test
244 showed there was possible publication bias among studies in resistin and visfatin
245 (Table 2). We used the trim-and-fill method to recalculate our pooled risk estimate of
246 resistin and visfatin. Meta-trim showed that corrected SMD (standard mean difference)
247 was not differ from uncorrected SMD, which suggested that publication bias had a
248 small effect on the final result. We did not assess the publication bias for apelin,
249 chemerin, irisin, omentin and vaspin based on the Cochrane Handbook for Systematic
250 Reviews of Interventions (www.cochranehandbook.org), which stated that the test for
251 publication bias yields unreliable results when less than ten studies were included in a
252 meta-analysis.

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254 **4.Discussion**

255 To our knowledge, this was the first systematic review and meta-analysis aimed
256 at quantifying the levels of nine kinds of adipokines in non-obese PCOS patients. This
257 systematic review and meta-analysis, including 81 studies demonstrated that
258 non-obese PCOS women showed a decreasing level of adiponectin and the increased
259 levels of leptin, visfatin, chemerin and resistin respectively. Our results indicated that
260 the concentration of common adipokines in plasma or serum changed remarkably in
261 non-obese PCOS women.

262 Over the past decade, a large number of studies had investigated the levels of
263 circulating adipokines in non-obese PCOS patients. Since the levels of adipokines
264 differed from the geographic regions, ethnicity or age, the results of studies were
265 inconsistent. For example, one Mahmoud A's paper showed lower levels of
266 adipokines in PCOS patients than in the control group¹⁸ whereas an Arikan's paper
267 showed the opposite result¹⁹. The purpose of meta-analysis was to integrate these
268 results for statistical analysis. Combining the findings of these studies was an
269 attractive option to enhance the credibility of the evidence²⁰. Therefore, we performed
270 a meta-analysis to reach a reliable conclusion on the changes of adipokines
271 concentration in non-obese PCOS patients.

272 Considering that studies had shown the levels of adipokines was related to BMI
273²¹ and there was evidence that PCOS patients had an increased BMI²², so the change
274 in adipokines levels might be caused by obesity rather than the PCOS itself. In this
275 meta-analysis, we only included the study on non-obese PCOS patients, so we could
276 exclude the influence of obesity and directly analyzed the relationship between PCOS
277 and adipokine levels.

278 Understanding the disturbance of adipokines levels in non-obese PCOS patients
279 help to explain the pathophysiology and symptoms of PCOS:(1). Hyperandrogenism: the
280 occurrence of PCOS was closely related to hyperandrogenism²³. Animal studies had
281 shown that impaired insulin sensitivity and glucose intolerance in mice (selectively
282 knocked down androgen receptors in adipocytes) were not related to obesity. Besides,
283 it was related to the changes of adipokines levels. Therefore, it could be presumed that

the AR (androgen receptor) in fat cells can control insulin sensitivity and glucose tolerance independently of obesity and affect adipokines levels in the meanwhile²⁴. In non-obese PCOS patients, androgen hypersecretion and androgen receptor dysfunction were the main symptoms, which might lead to the changes in adipokines levels²⁵. Meanwhile, some studies had shown that gender had a certain influence on the levels of adipokines in the body, so the increase of androgens in PCOS patients might lead to the change of the levels of adipokines in the body²⁶. (2). IR: there was the evidence that the occurrence of PCOS was closely related to IR²⁷. In vitro studies had shown that in vitro fat cells, certain adipokines activate protein kinases that increased insulin-mediated glucose transport, thus increasing insulin sensitivity through specific pathways, such as omentin²⁸. Meanwhile, some studies had shown the expression of proinsulin mRNA was inhibited by leptin in high level, which led to the decreased transcription activity of insulin gene promoter and the inhibited phosphorylation of insulin receptor matrix in peripheral tissues^{29, 30}. These studies suggested that IR might affect adipokines levels by increasing insulin levels. High leptin level could lead to IR in non-obese PCOS patients in the following possible ways: inhibition of phosphoenolpyruvate carboxykinase inhibited hepatic glucose oxidation and increased hepatic glycogen reserve; deposit of fat in skeletal muscle cells; breakdown of fat and the production of FFA (free fatty acids); direct inhibition of basal insulin secretion and glucose-stimulated insulin secretion. In addition, the insulin sensitizer thiazolidinedione could up-regulate the expression of adiponectin gene and promote the differentiation and apoptosis of adipocytes, thus reducing IR. Therefore, we inferred that disorders of adipokines levels played an important role in IR of non-obese PCOS patients. We might be able to treat PCOS with drugs that correct the disorder of adipokines levels. (3). Chronic inflammation: Chemerin, identified as an inflammatory factor at first, was thought to promote chemotaxis of immature dendritic cells and macrophages through its receptor CMKLR1³¹. CMKLR1 had been found to be expressed in many immune cells, including immature dendritic cells, myeloid dendritic cells, macrophages and natural killer cells^{32, 33}. This meant that chemerin and its receptor CMKLR1 were involved in the recruitment of different immune cells to the site of injury, and might affect the occurrence and development of inflammation. Adipokines and their receptors were elevated in many inflammatory states, suggesting that adipokines levels might be predictors of PCOS. Omentin had anti-inflammatory, anti-cardiovascular and anti-diabetic effects. Considering that obesity was a chronic low-grade inflammatory disease, long-term inflammatory stimulation might be one of the reasons for omentin's down-regulated expression.^{34, 35}.

In the long run, non-obese PCOS patients with disturbance of adipokine levels might lead to more related diseases, such as hypertension, coronary heart disease, type 2 diabetes, etc³⁶. Type 2 diabetes was almost 10 times more common in PCOS patients than in the normal population, and glucose intolerance was 30% to 50% higher in obese PCOS patients³⁷. PCOS in the future risk of cardiovascular disease (CVD) should not be ignored. PCOS was also closely related to IR, which could lead to a variety of cardiac metabolic abnormalities (such as dyslipidemia, high blood

328 pressure, glucose intolerance, diabetes and metabolic syndrome) that increased the
329 risk of cardiovascular disease in women³⁸.

330 Therefore, adipokines levels were of great significance in the diagnosis and
331 treatment of PCOS, and people should improve their understanding of abnormal
332 changes in adipokines levels. Metformin might alleviate corresponding symptoms and
333 treat PCOS by correcting abnormal levels of certain adipokines. For example, it could
334 reduce the levels of resistin, visfatin, irisin, chemerin and so on³⁹⁻⁴². A recent report
335 suggested that insulin and glucose affected the secretion of visfatin through
336 phosphatidylinositol 3-kinase and protein kinase B pathway⁴³. Metformin could
337 increase the sensitivity of peripheral tissues to insulin which help to reduce the
338 hyperinsulinemia caused by insulin resistance in PCOS patients. In the above ways,
339 metformin could alleviate the abnormal change of visfatin level. Moreover,
340 adipokines and hyperandrogenemia formed a vicious cycle of endocrine metabolism,
341 promoting the risk of PCOS and other related endocrine diseases. Metformin could
342 also relieve the symptoms of PCOS patients by reducing their high testosterone levels
343 through specific mechanisms⁴⁴. We presumed that metformin might be used to correct
344 the disorder of adipokine levels and thus to treat PCOS, but more experiments are
345 needed to prove.

346 Statistically, significant heterogeneity was found in the analysis of adiponectin,
347 apelin, chemerin, irisin, leptin, omentin, resistin, visfatin might reflect the clinical
348 heterogeneity and PCOS diagnostic criteria, different ethnic backgrounds, national
349 setting, age, or BMI. In addition, the BMI to determine obesity was different. This
350 suggested that caution should be exercised in extrapolating these results to more
351 extensive applications. However, the analysis of apelin showed no heterogeneity,
352 indicating that the included pieces of literature were homogeneous, and the study
353 results were accurate. Second, we found evidence of publication bias. Although a
354 trim-and-fill method suggested that unpublished trials might not influence the levels
355 of resistin and visfatin in non-obese patients with PCOS, these results should be
356 interpreted carefully.

357 Our literature search was comprehensive, and we did not apply any restrictions
358 on language to limit our ability to assess the relationship between the levels of
359 adipokines and PCOS. However, our meta-analysis still had some limitations. First of
360 all, there were many different test methods for the identification of PCOS, so the
361 diagnose of PCOS had heterogeneity. In addition, changes in adipokines levels in
362 normal weight or overweight PCOS patients were studied in this study, but we could
363 not entirely exclude all obese participants in the included study due to the different
364 criteria. Finally, there were many different methods to determine the levels of
365 adipokine in the blood, which may lead to some deviation. Despite these limitations,
366 the present meta-analysis had increased the statistical power by pooling the results of
367 single studies. Therefore, the total number of subjects was sufficiently large to support
368 our conclusion.

369 In summary, this systematic review and meta-analysis demonstrated that the
370 levels of circulating adipokines in non-obese PCOS patients with was changed to
371 varying degrees, which help to find potential pathogenesis and new biochemical

372 diagnostic criteria of PCOS. Moreover, this result might provide a new scheme to
373 treat PCOS by correcting disturbance of adipokines levels. However, further studies
374 were needed to explore the potential mechanism of the disturbance and focus on
375 whether the PCOS could be treated by correcting the levels of adipokines.

376 **Author's roles**

377 K.L. conducted literature search, complied data and drafted manuscript. X.S. and X.W.
378 contributed to literature search and data interpretation. H.W. reviewed manuscript and
379 provided advice. C.X contributed to critical discussion, reviewed all drafts of this article,
380 provided extensive advice, and revised the manuscript.

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385 **Conflict of Interest**

386 No conflict of interest to declare.

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516

517 **Captions for Tables and Figures:**

518 **Table 1. Characteristic of individual study included in the systematic review and
519 meta-analysis.**

520 Abbreviations: PCOS, polycystic ovary syndrome; BMI, body mass index; NA, not
521 available; NIH, National Institutes of Health.

522 **Table 2. Egger publication bias test for the adiponectin, leptin, visfatin and
523 resistin.**

524 Abbreviations: CI, confidence interval.

525 **Fig 1. Flow chart of study inclusion in systematic review and meta-analysis.**

526 **Fig 2. Meta-analysis of the association between the levels of adipokines in
527 non-obese patient and PCOS. Weights are from random effects analysis. A:
528 Meta-analysis of adiponectin. B: Meta-analysis of apelin. C: Meta-analysis of
529 chemerin. D: Meta-analysis of irisin.**

530 Abbreviations: PCOS, polycystic ovary syndrome; CI, confidence interval; SD,
531 standard difference.

532 **Fig 3. Meta-analysis of the association between the levels of adipokines in
533 non-obese patient and PCOS. Weights are from random effects analysis. A:
534 Meta-analysis of leptin. B: Meta-analysis of omentin. C: Meta-analysis of
535 resistin.**

536 Abbreviations: PCOS, polycystic ovary syndrome; CI, confidence interval; SD,
537 standard difference.

538 **Fig 4. Meta-analysis of the association between the levels of adipokines in
539 non-obese patient and PCOS. Weights are from random effects analysis. A:
540 Meta-analysis of vaspin. B: Meta-analysis of visfatin.**

541 Abbreviations: PCOS, polycystic ovary syndrome; CI, confidence interval; SD,
542 standard difference.

543 **Fig 5. Funnel plot analysis to detect publication bias under a dominant model. A:
544 Funnel plot for adiponectin; B: Funnel plot for leptin; C: Funnel plot for resistin;
545 D: Funnel plot for visfatin.**

546 Abbreviations: SE, standard error; SMD, standard mean difference.

547

Table I. characteristic of individual study included in the systematic review and meta-analysis.

Study	PCOS diagnosis Criteria	Region	Age (PCOS vs. controls)	BMI (kg/m ²) (PCOS vs. controls)	Primary conclusion
Ardawi (2005)	NIH Criteria	Saudi Arabia	25.9±5.8 ; 26.55±5.34	22.7±2.4 ; 22.4±1.8	Plasma adiponectin decreased in PCOS
Arikan (2009)	Rotterdam Criteria	Turkey	21.8±5.4 ; 24.9±5.7	23.8±6.6 ; 23.1±5.8	Serum adiponectin decreased and Serum leptin remained unchanged in PCOS
Baldani (2019)	Rotterdam Criteria	Croatia	26.4±5.9 ; 26.4±2.7	22.4±1.7 ; 21.8±1.8	Serum adiponectin decreased and Serum leptin and resistin increased in PCOS
Bannigida (2018)	Rotterdam Criteria	India	18 to 40	25.6±2.53 ; 21.2±4.86	Serum adiponectin decreased and Serum visfatin increased in PCOS
Behboudi (2017)	NIH Criteria	Iran	28.8±5 ; 30.9±6	21.8±1.9 ; 22±1.9	Serum visfatin decreased and Serum adiponectin, leptin, omentin, chemerin and resistin increased in PCOS
Continued table I					
Chen (2014)	Androgen Excess Society Criteria	Taiwan	25.1±5.7 ; 28.5±6.4	20.4±1.7 ; 20.2±2.1	Serum adiponectin increased and Serum leptin and resistin decreased in PCOS
Carmina (2005)	Classic criteria of hyperandrogenism and chronic anovulation	American	NA	22.7±0.4 ; 23±0.22	Serum adiponectin decreased and Serum leptin and resistin increased in PCOS
Ducluzeau (2003)	NA	France	21±3.3 ; 24.4±4.5	22.1±2.7 ; 22.9±5.1	Plasma adiponectin decreased and Plasma leptin remained unchanged in PCOS
Guven (2009)	Rotterdam Criteria	Turkey	15.7±1 ; 15.1±0.8	20.1±1 ; 20.1±1	Serum leptin and adiponectin remained unchanged in PCOS
Kim (2006)	Rotterdam Criteria	Korea	26.3±6.1 ; 25.5±5.3	21.3±1.8 ; 21.7±1.4	Serum adiponectin remained unchanged in PCOS
Kruszynska (2014)	Rotterdam Criteria	Poland	16 to 40 ; 17 to 40	21.03±1.83 ; 20.76±2.09	Plasma and Serum adiponectin decreased in PCOS
Lee (2013)	ESHRE/ASRM consensus	Korea	24±5 ; 24±4	21.9±2.0 ; 21.9±2.0	Plasma and Serum adiponectin decreased in PCOS
Nambiar (2016)	Rotterdam Criteria	India	28.71±5.49 ; 29.88±4.69	22.15±1.64 ; 21.83±1.772	Serum adiponectin decreased and Serum resistin increased in PCOS
Continued table I					
Olszanecka (2011)	Rotterdam Criteria	Poland	24.0±6.9 ; 27.8±7.1	22.1±2.4 ; 22.1±2.1	Plasma adiponectin decreased and Plasma resistin remained unchanged in PCOS
Olszanecka (2013)	Rotterdam Criteria	Poland	23.7±4.5 ; 23.8±4.3	21.3±2.2 ; 22.2±2.0	Plasma adiponectin remained unchanged in PCOS
Orio (2003)	Rotterdam Criteria	Italy	29.6±1.1 ; 29.8±1.1	22.1±0.3 ; 22.0±0.4	Plasma adiponectin remained unchanged in PCOS
Orio (2004)	NIH Criteria	Italy	NA	NA	Plasma adiponectin remained unchanged in PCOS
Panidis (2003)	Specific standards in the article	Greece	25.7±4.0 ; 27.8±4.9	21.6±1.6 ; 20.5±2.0	Serum adiponectin decreased in PCOS
pinhas (2009)	Rotterdam Criteria	Israel	15.5±1.7 ; 14.2±2.1	20.1 ± 2 ; 18.6±1.7	Serum adiponectin decreased in PCOS
Sharifi (2010)	Rotterdam Criteria	Iran	NA	NA	Serum adiponectin decreased in PCOS
Wang (2010)	Specific standards in the article	China	17 to 38 ; NA	NA	Serum adiponectin decreased and Serum resistin increased in PCOS
Yasar (2011)	Rotterdam Criteria	Turkey	17.45±0.99 ; 17.19±0.40	21.43±2.07 ; 18.64±1.58	Serum adiponectin decreased in PCOS

Continued table I

Yilmaz (2009)	Rotterdam Criteria	Turkey	NA	21.43±3.12 ; 20.89±3.21	Serum adiponectin decreased and Serum resistin increased in PCOS
Altinkaya (2014)	Rotterdam Criteria	Turkey	23.4±5.2 ; 24.1±4.9	22.4±1.5 ; 21.3±1.2	Serum apelin decreased in PCOS
olszanecka (2015)	Rotterdam Criteria	Poland	23.7±4.5 ; 23.8±4.3	21.3±2.2 ; 22.2±2.0	Plasma apelin increased in PCOS
Sun (2015)	Rotterdam Criteria	China	27.45±3.61 ; 26.70±4.40	21.80±1.89 ; 20.39±2.17	Serum apelin increased in PCOS
Ademoglu (2014)	Rotterdam Criteria	Turkey	24.0±4.8 ; 26.2±4.9	21.8±1.8 ; 21.3±2.7	Serum chemerin increased in PCOS
Foda (2019)	Rotterdam Criteria	Egypt	21 to 26 ; NA	24.64±0.36 ; 23.914±0.55	Serum chemerin increased in PCOS
Yang (2015)	Rotterdam Criteria	China	24.62±4.41 ; 3.73±3.39	20.86±2.16 ; 20.10±1.26	Serum chemerin increased in PCOS
Foda1 (2019)	Rotterdam Criteria	Egypt	NA	NA	Serum irisin increased in PCOS
Bousmpoula (2019)	Rotterdam Criteria	Greece	31.9±4.3 ; 35.1±4.5	22.2±1.1 ; 22.3±1.2	Serum irisin increased in PCOS
Continued table I					
Ali (2016)	Rotterdam Criteria	Iraq	NA ; 20 to 40	25.074±0.456;25.022±0.683	Serum irisin remained unchanged in PCOS
Foda (2018)	Rotterdam 2004	Egypt	28.25±2.08 ; 28.6±2.11	23.38 ± 0.34 ; 23.88±0.45	Serum irisin increased in PCOS
Macut (1997)	Specific standards in the article	Spain	24.3±1.56 ; 28.0±1.25	21.9±0.71 ; 21.01±0.58	Serum leptin remained unchanged in PCOS
Xiao (2006)	Obstetrics and gynecology, 6th edition	China	27.7±3.56 ; 28.35±2.98	21.63±2.8 ; 20.51±1.45	Serum leptin increased in PCOS
Daghestani (2018)	Rotterdam Criteria	Saudi Arabia	25.61±0.39 ; 24.67±0.50	22.86±0.20 ; 20.85±0.24	Serum leptin remained unchanged in PCOS
Demirel (2007)	NIH Criteria	Turkey	15.5±0.9 ; 15.5±1.3	21.6±2.4 ; 21.1±2.1	Serum leptin increased in PCOS
Elorabi (1999)	NA	Egypt	NA	NA	Serum leptin increased in PCOS
Erel (2003)	Specific standards in the article	Turkey	22.0±3.5 ; 28.0±5.4	21.5±2.2 ; 20.8±2.0	Serum leptin remained unchanged in PCOS
Garruti (2014)	ESHRE/ASRM consensus	Italy	32.09±3.60 ; 34.35±3.13	22.55±2.61 ; 22.55±2.55	Serum leptin increased in PCOS
Continued table I					
Hahn (2006)	NIH Criteria	Germany	27.0±5.6 ; 25.0±4.0	21.0±1.9 ; 21.5±2.0	Serum leptin decreased in PCOS
Jeon (2013)	Rotterdam Criteria	Korea	23.88±4.86 ; 24.92±2.94	20.23±2.19 ; 19.77±1.51	Serum leptin increased in PCOS
Mancini (2009)	Specific standards in the article	Italy	18 to 35 ; NA	NA	Serum leptin decreased in PCOS
Mendonca (2004)	NIH Criteria	Brazil	20.0±5.2 ; 30.0±6.3	23.2±2.3 ; 22.3±2.2	Serum leptin remained unchanged in PCOS
Ram (2005)	Specific standards in the article	India	18 to 44	20.0 ± 1.42 ; 19.0 ± 1.02	Serum leptin increased in PCOS
Yildizhan (2011)	Rotterdam Criteria	Turkey	25.70±3.70 ; 25.44±2.62	23.85±1.1 ; 23.88±3.83	Serum leptin increased in PCOS
Takeuchi (2000)	Specific standards in the article	Japan	26.3±1.3 ; 26.9±1.6	19.4±0.5 ; 19.0±0.5	Serum leptin remained unchanged in PCOS
Li (2009)	Rotterdam Criteria	China	25±5 ; 26±7	20.3±1.9 ; 20.6±2.1	Serum leptin and adiponectin remained unchanged in PCOS
Cheng (2014)	Rotterdam Criteria	China	28.3±9.2 ; 28.6±9.4	22.4±2.5 ; 21.9±2.6	Serum leptin increased in PCOS

Continued table I

Güne (2015)	Androgen Excess Society Criteria	Turkey	NA	22.65±2.05 ; 21.41±3.44	Serum omentin decreased in PCOS
Guvenc (2016)	Rotterdam Criteria	Turkey	25.40±5.62 ; 31.50±7.59	24.87±5.02 ; 23.7±4.46	Serum vaspin, chemerin and omentin remained unchanged in PCOS
Wang (2012)	Rotterdam Criteria	China	25.7±4.5 ; 26.8±4.7	21.6±2.6 ; 21.7±1.9	Serum resistin remained unchanged in PCOS
Farshchian (2014)	NIH Criteria	Iran	28.3±5.1 ; 28.3±4.8	22.5±1.7 ; 22.4±1.8	Serum resistin and visfatin remained unchanged in PCOS
Panidis(2004)	Specific standards in the article	Greece	25.7±4.0 ; 28.6±4.5	21.6±1.6 ; 21.6±1.9	Serum resistin remained unchanged in PCOS
Pangaribuan (2011)	Rotterdam Criteria	Indonesia	25.6±6.1 ; 22.2±2.1	22.0±1.7 ; 20.6±2.1	Serum resistin remained unchanged in PCOS
Koreczala (2008)	ESHRE/ASRM consensus	Poland	22±2.5 ; 21±2.3	21±0.9 ; 22±1.3	Serum resistin remained unchanged in PCOS
Dikmen (2011)	Rotterdam Criteria	Turkey	21.11±2.59 ; 22.70±2.25	22.36±2.88 ; 20.64±2.12	Serum resistin decreased in PCOS
Seow (2007)	Rotterdam Criteria	Taiwan	32.2±3.5 ; 28.3±3.3	21.1±1.7 ; 22.5±14.9	Serum resistin remained unchanged in PCOS

Continued table I

Akbarzadeh (2012)	Rotterdam Criteria	Iran	21.68±4.01 ; 24.06±6.58	22.58±2.14 ; 21.87±1.83	Serum vaspin decreased in PCOS
koiou1 (2011)	Rotterdam Criteria	Greece	19.9±3.0 ; 31.3±4.5	23.2±4.4 ; 21.9±1.6	Serum vaspin increased in PCOS
Gümüş (2014)	Rotterdam Criteria	Turkey	18.80±2.20 ; 19.61±2.41	24.06±5.22 ; 21.30±3.89	Serum visfatin remained unchanged in PCOS
Dikmen (2010)	Rotterdam Criteria	Turkey	21.1±2.5 ; 22.7±2.2	22.3±2.8 ; 20.6±2.1	Serum visfatin increased in PCOS
Güdücü (2012)	Rotterdam Criteria	Turkey	24.03±4.08 ; 27.70±5.06	21.03±1.94 ; 23.45±5.32	Serum visfatin remained unchanged in PCOS
Tsouma (2014)	Rotterdam Criteria	Greece	31.0 (24.0–41.0) ; 31.6 (26.0–42.0)	22.2 (20.4–24.5) ; 22.5 (20.0–24.5)	Serum visfatin increased in PCOS
Cassar (2014)	Rotterdam Criteria	Australia	27±4 ; 28±6	23±2 ; 22±2	Serum visfatin remained unchanged in PCOS
Gen (2009)	Rotterdam Criteria	Turkey	21.85±4.06 ; 23.46±5.15	20.74±1.75 ; 20.85±2.08	Serum visfatin remained unchanged in PCOS
Kowalska (2007)	Rotterdam Criteria	Poland	23.69±3.46 ; 26.24±6.00	21.39±2.10 ; 21.81±2.00	Serum visfatin increased in PCOS

Continued table I

Olszanecka (2012)	Rotterdam Criteria	Poland	23.7±4.5 ; 23.8±4.3	21.3±2.2 ; 22.2±2.0	Plasma visfatin decreased in PCOS
Panidis (2008)	NIH Criteria	Greece	23.78±0.95 ; 24.31±0.90	22.09±0.41 ; 21.62±0.38	Serum visfatin increased in PCOS
Plati (2010)	Rotterdam Criteria	Greece	32.3±4.0 ; 32.9±4.3	22.41±0.21 ; 22.5±0.2	Serum visfatin decreased in PCOS
Pekcan (2019)	Rotterdam Criteria	Turkey	21.81±3.78 ; 22.97±4.16	22.10±2.91 ; 21.58±2.81	Serum adiponectin decreased in PCOS
Daan (2016)	Rotterdam Criteria	Netherlands	28.8 (25.8–31.2) ; 34.5 (30.7–37.7)	21.8 (19.8–22.2) ; 22.5 (21.2–24.5)	Serum adiponectin increased in PCOS
Mirza (2014)	Rotterdam Criteria	Pakistan	25.7±6 ; 25.4±6.7	19.3±2.6 ; 18.3±2.4	Serum adiponectin decreased in PCOS
Orlik (2014)	Rotterdam Criteria	Poland	23.7±4.5 ; 23.8±4.3	20.6 (19.6–22.7) ; 22.4 (21.0–24.0)	Serum adiponectin decreased in PCOS
Seow (2009)	Rotterdam Criteria	Taiwan	30.1 ± 4.4 ; 27.6 ± 3.3	21.3 ± 5.83 ; 22.8 ± 5.6	Serum adiponectin decreased in PCOS
Svendsen (2012)	Rotterdam Criteria	Denmark	NA	NA	Plasma adiponectin decreased in PCOS

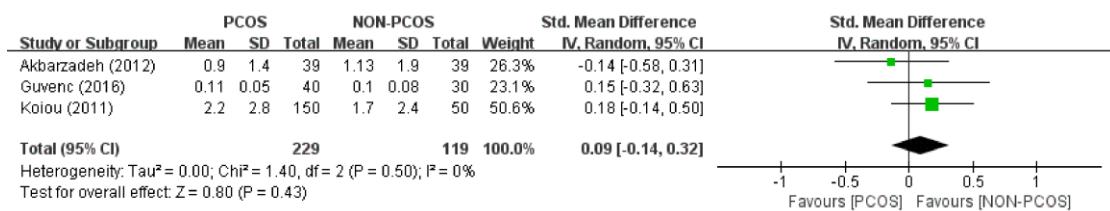
Continued table I

Lecke(2011)	Rotterdam Criteria	Brazil	$25.4 \pm 5.3 ; 29.3 \pm 5.9$	$22.5 \pm 2.3 ; 22.5 \pm 1.9$	Serum leptin increased in PCOS
Rizk (2015)	NIH Criteria	Qatar	$21 \pm 1.3 ; 21.1 \pm 1.85$	$20.867 \pm 2.41 ; 20.93 \pm 3.03$	Serum leptin increased in PCOS
Telli (2002)	Rotterdam Criteria	Turkey	$21.4 \pm 2.74 ; 22.71 \pm 5.44$	$23.9 \pm 4.91 ; 22.06 \pm 3.98$	Serum leptin increased in PCOS
Lu (2005)	Specific standards in the article	China	$30 (29.0-32.5) ;$ $30 (29.0-32.8)$	$21.6 \pm 2.0 ; 21.4 \pm 2.2$	Serum leptin increased in PCOS
Gul (2015)	Rotterdam Criteria	Turkey	$23.7 \pm 3.1 ; 29.8 \pm 4.1$	$22.5 \pm 2.0 ; 24.2 \pm 2.7$	Plasma visfatin and resistinin remained unchanged in PCOS

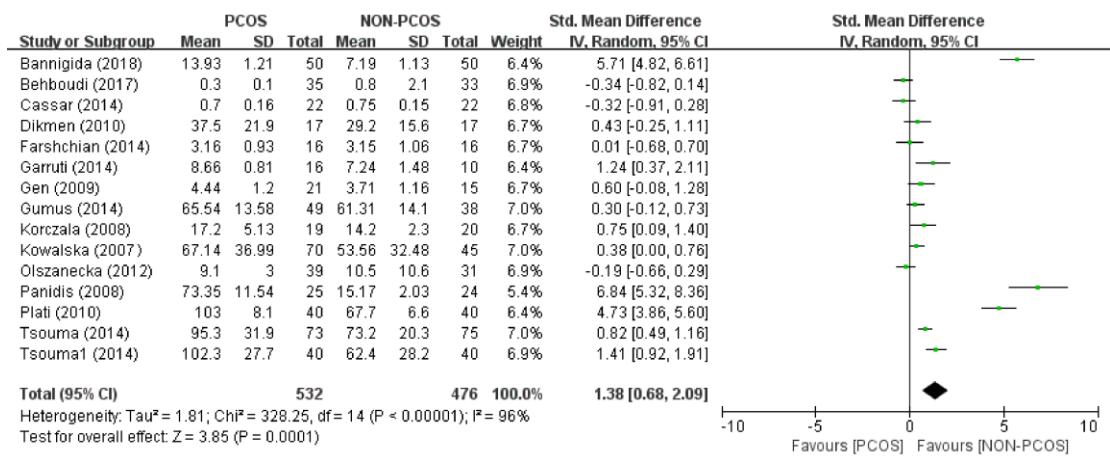
Table II. Egger publication bias test for the adiponectin, leptin, visfatin and resistin.

Indices	No. of studies	Coefficient	Standard Error	t	P	95%CI
adiponectin	30	-3.45	1.98	1.75	0.092	-7.50 to 0.60
leptin	25	0.45	1.54	0.29	0.775	-2.75 to 3.64
visfatin	15	8.39	3.11	2.7	0.018	1.67 to 15.11
resistin	18	-6.48	1.95	3.33	0.004	-10.61 to -2.35

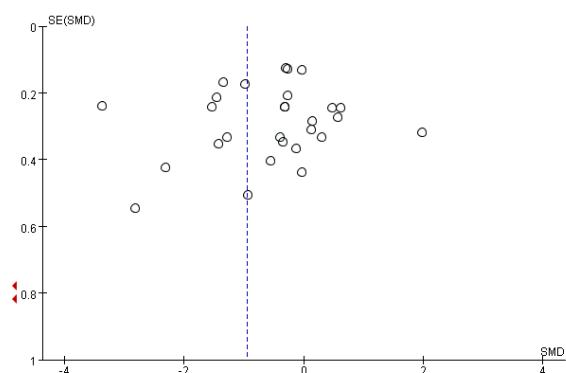
A



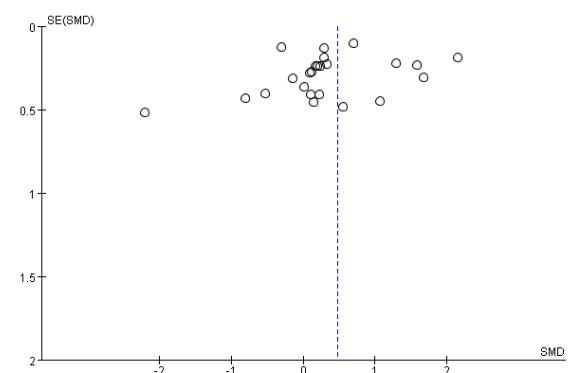
B



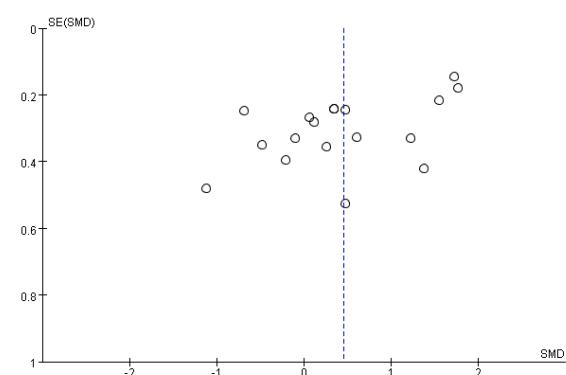
A: Funnel plot for adiponectin



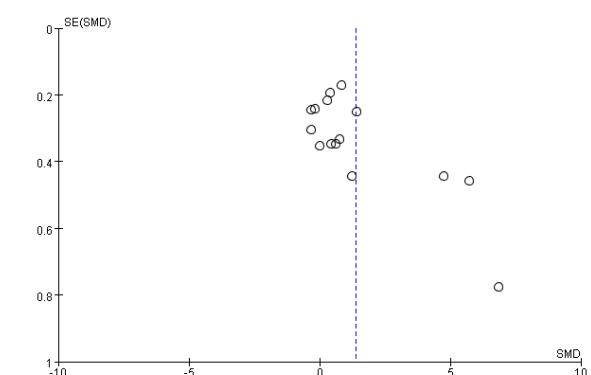
B: Funnel plot for leptin



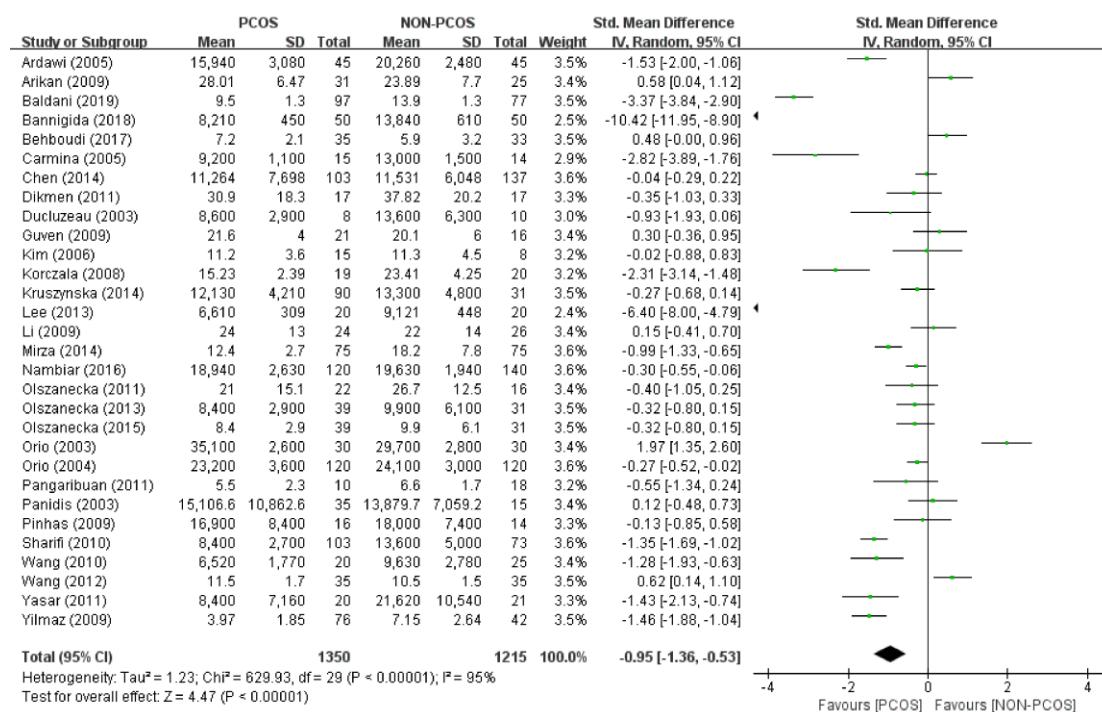
C: Funnel plot for resistin



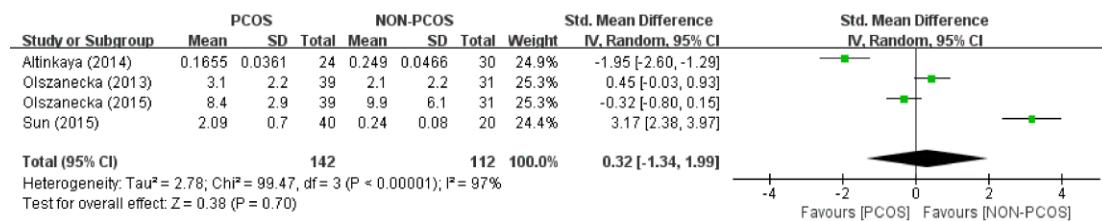
D: Funnel plot for visfatin



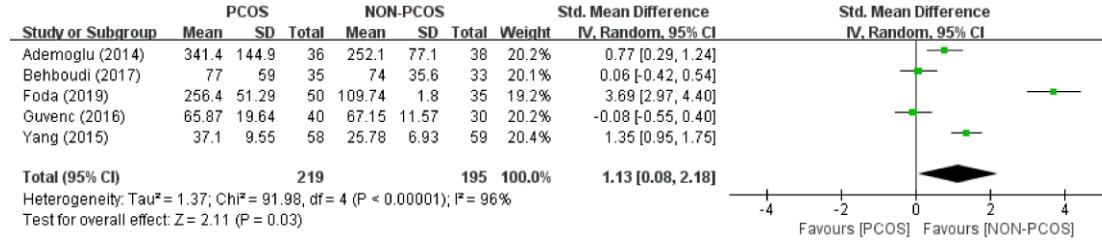
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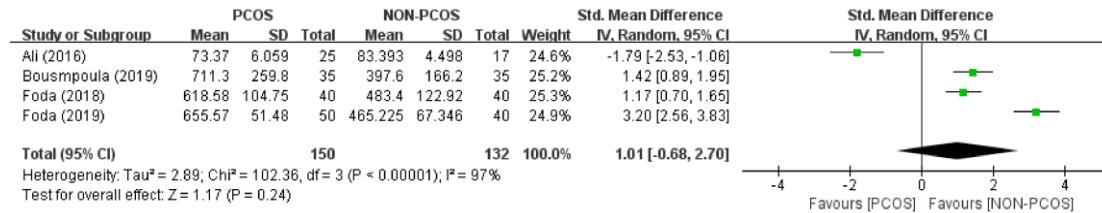
B



C



D



identification

Records identified through Pubmed searching (n=530)

Records identified through Embase searching (n=414)

Records identified through Web of sci searching (n=1912)

screening

Records after duplicates removed (n=1540)

Records screened by browsing the title and abstract (n=284)

203 articles were excluded for:
(1).Researches without control group.
(2).Subjects in researches were obesity.

Full text articles assessed for eligible (n=81)

81 articles included in quantitative and qualitative analysis

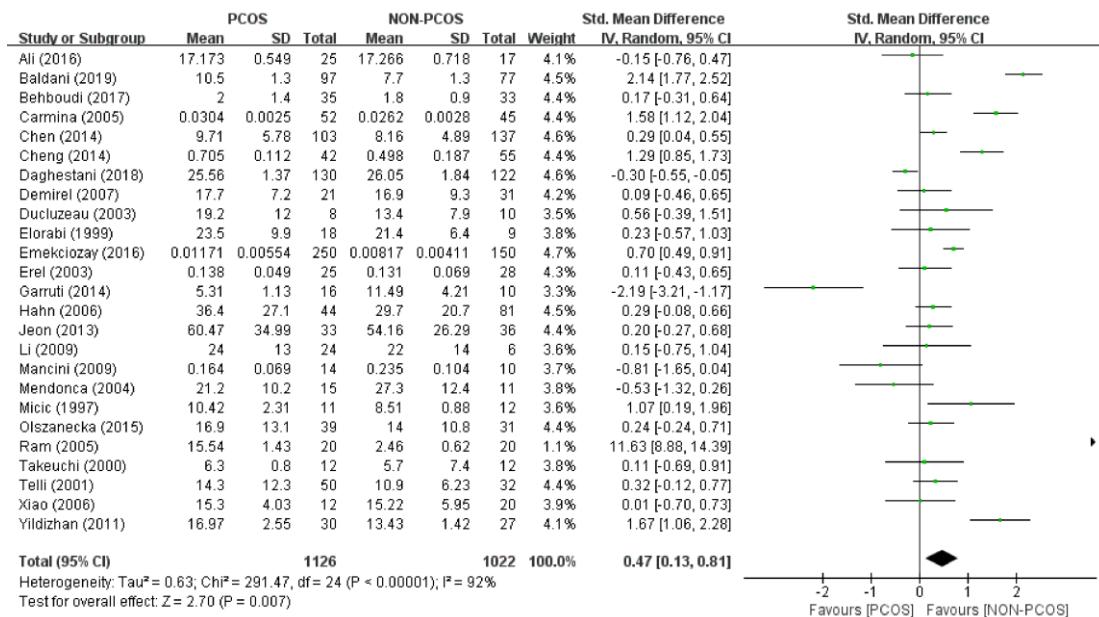
10 articles were excluded for:
(1).Researches did not provide the data as mean±SD.

71 articles included in quantitative and qualitative analysis

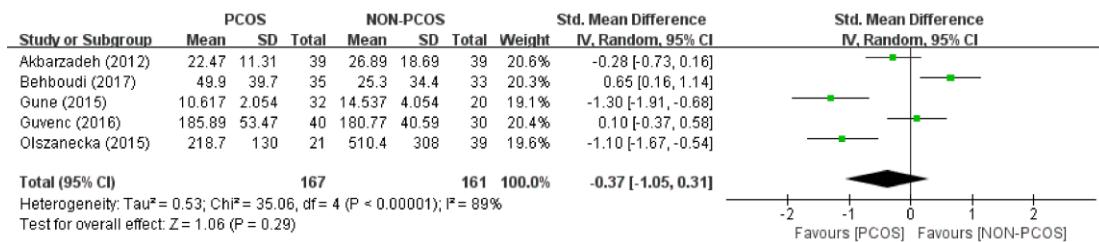
eligible

inclusion

A



B



C

