



## Review Article

## Correlation of clinical, radiological and serum analysis of hypovitaminosis D with polycystic ovary syndrome: A systematic review and meta-analysis



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### المخلص

**أهداف البحث:** يؤدي نقص فيتامين د<sup>د</sup> إلى عدد من المشاكل الصحية التي تشمل القلب، والأوعية الدموية، والنظام الأيضي، والغدد الصماء، واضطرابات الجهاز العصبي والأمراض السرطانية. إلا أن دور نقص فيتامين د<sup>د</sup> كمسبب بدوره في مرض متلازمة المبيض المتعدد الأكياس غير واضح. هدفت هذه الدراسة إلى قياس تأثير نقص فيتامين د<sup>د</sup> على متلازمة المبيض المتعدد الأكياس بصورة موضوعية عن طريق تقييم كمي للدراسات الأصلية التي درست مرضى متلازمة المبيض المتعدد الأكياس وما يقابلهم من غير المصابين.

**طرق البحث:** تم البحث في قواعد بيانات كل من "مدلاين" و"اسكو" و"ساينس داركت" و"سينال" عن الدراسات الأصلية السريرية المنشورة بكاملها باللغة الإنجليزية خلال الفترة ٢٠٠٦ - ٢٠١٦ التي بحثت في ارتباط نقص فيتامين د<sup>د</sup> بمتلازمة المبيض المتعدد الأكياس والمصحوبة ببيانات المصابين وغير المصابين بمتلازمة المبيض المتعدد الأكياس باستخدام برنامج إنذونات إكس 7.

**النتائج:** وُجد أن عشر دراسات كانت مؤهلة لهذا التحليل البعدي. ويعطي ملخص التأثير لهذا التحليل البعدي صورة عن قيمة مقدارها -٠,٤٥، مع فاصل ثقة -١,٦٨ إلى ٠,٧٩. مما يدعم فرضية أن تركيزات أقل من فيتامين د<sup>د</sup> في الدم تمثل وضعية محدد مشارك يؤثر على الاضطرابات الهرمونية والأبضية في متلازمة المبيض المتعدد الأكياس.

**الاستنتاجات:** ترتبط التركيزات الأقل من فيتامين د<sup>د</sup> في الدم بمخاطر أكبر بالإصابة بمتلازمة المبيض المتعدد الأكياس. إلا أنه يبقى تحديد التأثيرات العلاجية لفيتامين د<sup>د</sup> على متلازمة المبيض المتعدد الأكياس بتدخلات مستقبلية تدخلية.

**الكلمات المفتاحية:** فيتامين د<sup>د</sup>؛ ٢٥-هيدروكسي فيتامين د<sup>د</sup>؛ متلازمة المبيض المتعدد الأكياس؛ الاضطرابات الأبضية

### Abstract

**Objectives:** Vitamin D deficiency leads to a myriad of healthcare problems from cardiovascular, metabolic, endocrine, and neurological disorders to cancer. However, the role of vitamin D deficiency in the etiopathogenesis of polycystic ovary syndrome (PCOS) is unclear. This study aimed to measure objectively the impact of vitamin D deficiency on PCOS through a quantitative assessment of the existing literature.

**Methods:** We conducted a systematic search of published literature on the following online databases using EndnoteX7: MEDLINE, EBSCO, ScienceDirect, and CINAHL. Searches were limited to full-text English-language journal articles published between 2006 and 2016. Eligible clinical studies employed control group data to investigate the association between vitamin D deficiency and PCOS.

**Results:** We identified 10 studies eligible for this meta-analysis. The summary intervention effect calculated for this meta-analysis yields a value of -0.45 with a confidence interval of -1.68 to 0.79, supporting the hypothesis that lower concentrations of serum vitamin D play a role in the hormonal and metabolic dysregulation seen in PCOS.

**Conclusions:** Lower concentrations of serum vitamin D are associated with a greater risk of developing PCOS. However, the therapeutic effect of vitamin D in the setting of PCOS remains unclear and must be determined by future interventional studies.

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**Keywords:** 25-Hydroxyvitamin D; Metabolic disorders; Polycystic ovary syndrome; Vitamin D

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## Introduction

Serum 25(OH)D is considered to be the end-point functional indicator of vitamin D levels in the human body.<sup>1</sup> Concentrations of 25(OH)D in the range of 50–74 nmol/L (20–30 ng/mL) refers to vitamin D insufficiency, whereas a threshold value of less than 50 nmol/L (20 ng/mL) is widely accepted as vitamin D deficiency.<sup>2</sup> In addition to its established role in the aetiology of osteomalacia and rickets, vitamin D deficiency has also been implicated in the etiopathogenesis of disorders such as cardiovascular disease,<sup>3</sup> colorectal cancer (including changes in subsite distribution),<sup>4–7</sup> breast cancer,<sup>8</sup> depression,<sup>9</sup> benign gallbladder affections,<sup>10</sup> autoimmune thyroid disease,<sup>11</sup> and diabetes mellitus.<sup>12,13</sup>

A number of recently published empirical studies have demonstrated that vitamin D deficiency, and its associated calcium dysregulation play a key role of in the aetiology of metabolic risk factors for PCOS.<sup>14,15</sup> PCOS is a complex syndrome with serious reproductive and metabolic implications commonly manifested as a clinical presentation consisting of menstrual irregularity, hirsutism, acne, infertility, and alopecia.<sup>16</sup> According to the recommendations of the revised Rotterdam consensus group, two of the following three criteria are sufficient for the diagnosis of PCOS: 1) Oligo- and/or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, 3) polycystic ovaries and 4) the exclusion of other aetiologies (e.g., congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome).<sup>17</sup> In addition, the polycystic ovarian morphology in PCOS has been defined as “the presence of 12 or more follicles, measuring between 2 and 9 mm, throughout the entire ovary and/or an ovarian volume 10 cm<sup>3</sup>”.<sup>17</sup> Although transvaginal ultrasound is considered to be the gold standard for the evaluation of suspected PCOS, poor visualization of the ovaries of obese women and the procedure's contraindication in unmarried women limit its universal application.<sup>18</sup> Magnetic resonance imaging (MRI) is a promising alternative and has been employed for the assessment of PCOS in adolescents. MRI-generated 6 mm slice thickness images (using 1.5 or 3 T and axial or angled-axial echo-train spin technology) can delineate follicle size, antral follicle count per ovary, and ovarian volume.<sup>19</sup> The mean antral follicle count per ovary and ovarian volume are significantly greater in women with PCOS than the non-PCOS controls.<sup>20</sup> In addition, MRI can show striking differences between girls with and without PCOS, aiding the diagnose of PCOS in unmarried girls for whom transvaginal ultrasound is contraindicated. However, other studies have cautioned against the use of MRI alone in diagnosis of PCOS because the morphological features PCOS and non-PCOS subjects can overlap. Instead, a

multi-dimensional approach integrating clinical, biochemical, and radiological modalities has been proposed.<sup>21,22</sup>

Although the precise pathogenetic mechanism of PCOS is debatable, it is believed to be a heterogeneous disorder with both genetic and environmental components.<sup>23,24</sup> It has been suggested that Vitamin D influences the production pattern of ovarian granulosa cells by blunting follicle stimulating hormone (FSH) sensitivity, thereby playing a role in ovarian follicle development.<sup>25</sup> Several studies have reported an inverse relationship between vitamin D status and metabolic disturbances in PCOS patients.<sup>26,27</sup> In their observational study of 52 patients (25 PCOS and 27 control), Li et al. investigated the potential correlation between Vitamin D deficiency and PCOS.<sup>14</sup> The researchers found vitamin D deficiency in 44.0% and 11.2% of patients in the PCOS and control groups, respectively ( $p = 0.47$ ).

Although a great many studies have investigated the link between vitamin D status and the metabolic and hormonal derangements seen in PCOS, whether this association is one of cause and effect remains unclear. Despite a staggering increase in the number of interventional studies investigating the impact of vitamin D supplementation on PCOS, inadequate data exists to convincingly establish a causal link, primarily due to the small sample size of the studies. This systematic review and meta-analysis quantitatively summarizes the currently available research to determine whether serum vitamin D levels are lower in women with PCOS compared to those without PCOS.

## Study design

### *Search strategy and studies inclusion criteria*

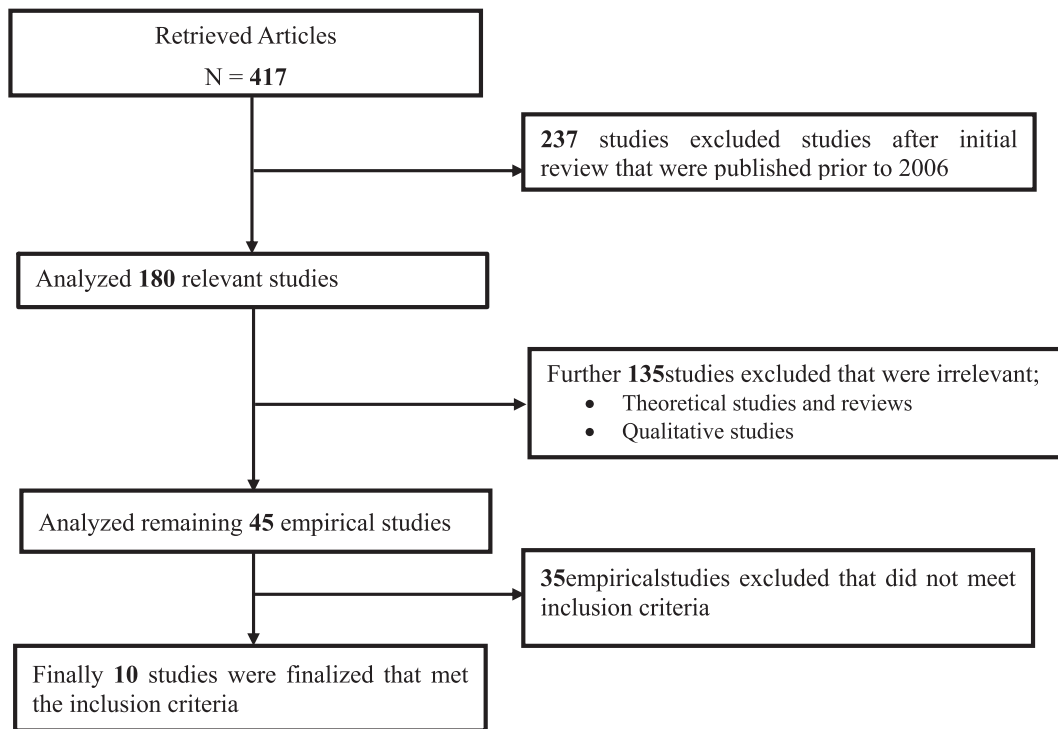
We conducted a systematic search of published literature in August 2016. Searches were limited to full-text English-language journal articles published between 2006 and 2016. Eligible clinical studies investigated the association of vitamin D deficiency and PCOS and employed a control group in the study design. We searched the databases of MEDLINE, EBSCO, ScienceDirect, and CINAHL for the retrieval of relevant studies by connecting the MeSH terms “PCOS” AND “25-(OH)D” AND/OR “vitamin D” using EndnoteX7.

### *Study exclusion criteria*

Editorial and review articles, short notes, conference proceedings, letters to editors, and personal opinions were excluded from the study. This search retrieved 417 citations, as shown in Figure 1. The preferred reporting items for systematic review and meta-analysis protocols (PRISMA) were used to describe the rationale, hypothesis, and, planned methods of the review.<sup>28</sup>

### *Data extraction, analysis and synthesis*

During the initial review, 237 studies were excluded, because they were found to be duplicated, and others because they were published prior to 2006. Subsequently, a review of titles and abstracts lead to the exclusion of another 135



**Figure 1:** Flow chart showing the stepwise algorithm used during the selection of studies in this meta-analysis and systematic review.

studies because they were irrelevant and did not fulfil the inclusion criteria. During the full text analysis of the relevant 45 studies, 35 were further excluded due to inappropriate or incomplete data for this meta-analysis. Therefore, the following 10 relevant studies were finalized as having met the eligibility criteria.

1. Wehr E, Trummer O, Giuliani A, Gruber HJ, Pieber TR, Obermayer-Pietsch B. Vitamin D-associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome. *European journal of endocrinology*. 2011 May 1;164(5):741–9.<sup>29</sup>
2. Savastano S, Valentino R, Di Somma C, Orio F, Pivonello C, Passaretti F, Brancato V, Formisano P, Colao A, Beguinot F, Tarantino G. Serum 25-Hydroxyvitamin D Levels, phosphoprotein enriched in diabetes gene product (PED/PEA-15) and leptin-to-adiponectin ratio in women with PCOS. *Nutrition & metabolism*. 2011 Nov 23;8(1):1.<sup>30</sup>
3. Amal S, Shalaby SM, Aly NM, Rashad NM, Abdelaziz AM. Genetic variation in the vitamin D receptor gene and vitamin D serum levels in Egyptian women with polycystic ovary syndrome. *Molecular biology reports*. 2013 Nov 1;40(11):6063–73.<sup>31</sup>
4. Li HW, Brereton RE, Anderson RA, Wallace AM, Ho CK. Vitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndrome. *Metabolism*. 2011 Oct 31;60(10):1475–81.<sup>14</sup>
5. Hassan NE, El-Orabi HA, Eid YM, Mohammed NR. Effect of 25-hydroxyvitamin D on metabolic parameters and insulin resistance in patients with polycystic ovarian

syndrome. *Middle East Fertility Society Journal*. 2012 Sep 30;17(3):176–80.<sup>32</sup>

6. Mahmoudi T, Gourabi H, Ashrafi M, Yazdi RS, Eza-badi Z. Calcitropic hormones, insulin resistance, and the polycystic ovary syndrome. *Fertility and sterility*. 2010 Mar 1;93(4):1208–14.<sup>33</sup>
7. Mazloomi S, Sharifi F, Hajhosseini R, Kalantari S, Mazloomzadeh S. Association between hypo-adiponectinemia and low serum concentrations of calcium and vitamin D in women with polycystic ovary syndrome. *ISRN endocrinology*. 2012 Jan 16;2012.<sup>34</sup>
8. Ngo DT, Chan WP, Rajendran S, Heresztyn T, Amarasekera A, Sverdlow AL, O'Loughlin PD, Morris HA, Chirkov YY, Norman RJ, Horowitz JD. Determinants of insulin responsiveness in young women: impact of polycystic ovarian syndrome, nitric oxide, and vitamin D. *Nitric Oxide*. 2011 Oct 30;25(3):326–30.<sup>35</sup>
9. Kim JJ, Choi YM, Chae SJ, Hwang KR, Yoon SH, Kim MJ, Kim SM, Ku SY, Kim SH, Kim JG. Vitamin D deficiency in women with polycystic ovary syndrome. *Clinical and experimental reproductive medicine*. 2014 Jun 1;41(2):80–5.<sup>36</sup>
10. Figuurová J, Dravecká I, Javorský M, Petříková J, Lazúrová I. Prevalence of vitamin D deficiency in Slovak women with polycystic ovary syndrome and its relation to metabolic and reproductive abnormalities. *Wiener klinische Wochenschrift*. 2015 Mar 19:1–8.<sup>37</sup>

Two independent researchers reviewed and analysed the data during the entire literature review, data extraction, synthesis, and analysis. Discrepancies and differences were resolved by discussion, mutual consensus, and arbitration. A

detailed overview and executive summary of the key findings of the selected 10 studies are provided in [Appendix 1](#).

A Forest plot was used for the meta-analysis of the 10 studies included in this review. The forest plot graphically represents the consistency and reliability of the results of a selected set of studies. In our study, the Forest plot was designed using Review Manger 5.3 software, developed by Cochrane Library.<sup>38</sup> In this plot, the effect size of each study is computed as an outcome and the pooled effect size is calculated to estimate the heterogeneity of the included studies. A Q test was used to check the heterogeneity in selected studies, with a null hypothesis of “all studies are identical.” The I squared ( $I^2$ ) statistic objectively ensures the quantity of heterogeneity in percentage terms and quantitatively asserts the consistency of the selected studies.<sup>39</sup> After carefully analysing the heterogeneity of the studies, the appropriate summary intervention effect model was used to determine both the fixed effects and random effects models. A fixed effects model is useful in the case of low heterogeneity, whereas a random effects model becomes useful when heterogeneity is greater. The level of significance in this study is 5% ( $p < 0.05$ ).

## Results

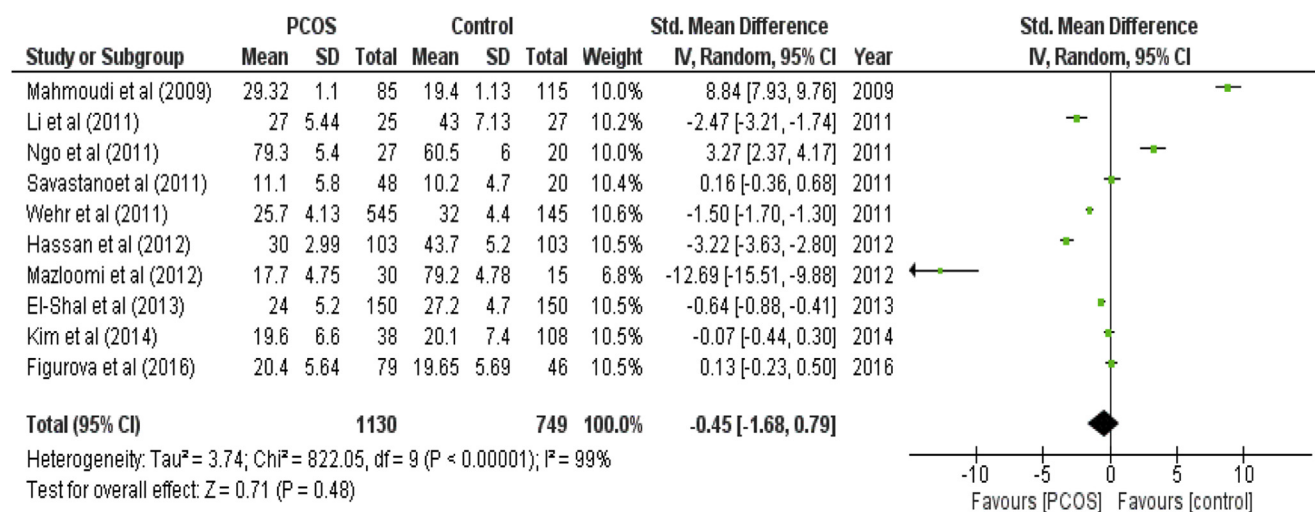
The Forest plot illustrated in [Figure 2](#) shows a series of estimates and their confidence intervals at 95%. Each individual study's effect size (outcome) is shown by a square the confidence interval is represented by a horizontal line. At first glance, this plot demonstrates wide confidence intervals and inconsistent response rates that would seem to indicate heterogeneity. For statistical confirmation, both the Q and  $I^2$  statistics were calculated. The Z test value of 0.71 is not statistically significant but the Cochran Q ( $\text{Chi}^2 = 822.05$ ) test result is significant at 1% level of significance. Therefore, the studies are not identical.  $I^2$  is 99% which indicates the presence of significant heterogeneity across the studies. On the basis of greater heterogeneity, a random effects model was the most appropriate model to use in this study. The summary effect, represented by a diamond in the figure, has a value

of  $-0.45$  with a confidence interval of  $-1.68$  to  $0.79$ , supporting the hypothesis that vitamin D concentrations are lower in PCOS patients compared to their counterpart control group.

## Discussion

The results of this meta-analysis indicate that the concentration of 25(OH)D were significantly lower in the PCOS group than in the control group, as suggested by a summary intervention effect of  $-0.45$  with a confidence interval ranging from  $-1.68$  to  $0.79$ . 25(OH)D concentration is the primary indicator of vitamin D status in the human body. Since Hypovitaminosis is associated with metabolic syndrome and its component characteristics (e.g., obesity, insulin resistance, and glucose intolerance),<sup>40</sup> it has been suggested that 25(OH)D is also associated with PCOS. Our results highlight the inverse relationship between the concentration of 25(OH)D and the development of PCOS. These findings are in agreement with previously published studies in finding lower levels of 25(OH)D in women with PCOS than women without the condition.<sup>14,41,42</sup> These findings may underscore a possible link between vitamin D and androgens or sex hormone binding globulin (SHBG).<sup>43</sup>

Many published articles have emphasized the association of hypovitaminosis D and insulin resistance, metabolic and hormonal disturbances in PCOS, and obesity, but the common link between these deregulatory pathways is not yet clear. Some studies have shown convincing data that suggests PCOS patients have impaired insulin sensitivity and an elevated risk for insulin resistance.<sup>35,44,45</sup> One possible explanation is that vitamin D might directly increase insulin sensitivity by stimulating the expression of insulin receptors in peripheral tissues.<sup>46</sup> In addition, Ardabili et al. have hypothesized another distinct pathway in which vitamin D deficiency may also disrupt extracellular and intracellular calcium homeostasis, consequently interfering with insulin secretion.<sup>47</sup> The resulting change in the intracellular calcium concentration of peripheral tissues could potentially lead to peripheral insulin resistance.<sup>48</sup> Finally, vitamin D levels might also promote insulin



**Figure 2:** Meta-analysis of the studies investigating the association of vitamin D deficiency and polycystic ovary syndrome.

resistance through the renin–angiotensin–aldosterone pathway. There is also sufficient clinical evidence to suggest that nitric oxide suppresses insulin resistance and, conversely, the impairment of NO production could potentially lead to insulin resistance.<sup>49,50</sup>

Vitamin D plays a significant role in the pathogenesis of insulin resistance,<sup>51</sup> which is thought to protect patients with PCOS from osteoporosis, whereas elevated cortisol levels, low growth hormone, and amenorrhea may be associated with decreased bone mineral density.<sup>52</sup> Recent studies have suggested that insulin resistance in PCOS is associated with lower vitamin D concentrations, a finding difficult to ascribe to obesity alone.<sup>53,54</sup> Hypothetically, “therapeutic use of Vitamin D may therefore have positive effects on insulin sensitivity and perhaps also hyperandrogenemia in patients with PCOS”.<sup>55</sup> Research has shown an inverse relationship between 25(OH)D and waist circumference in both children<sup>56,57</sup> and adults.<sup>58</sup> Worstman et al. have argued that obesity-associated vitamin D insufficiency is potentially related to the suboptimal bioavailability of vitamin D<sub>3</sub> from cutaneous and dietary sources due to its accumulation in cutaneous depots.<sup>59</sup>

Kim et al. have attempted to find the association between hypovitaminosis D and the development of PCOS and report that the prevalence of vitamin D deficiency is equally common among both patients and controls.<sup>36</sup> Similarly, other studies were unable to find any correlation between low serum vitamin D and clinical or metabolic manifestations of PCOS, thus failing to elucidate a convincing role for vitamin D deficiency in the pathogenesis of PCOS.<sup>60,61</sup>

## Conclusions

This systematic review and meta-analysis demonstrates a strong association between lower concentrations of vitamin D and PCOS. There is a great propensity towards vitamin D deficiency in women with PCOS. Although an entire body of literature suggests an association between vitamin D deficiency and the etiopathogenesis of insulin resistance, altered ovarian steroidogenesis, and obesity, the therapeutic role of vitamin D remains to be proved by future clinical studies. This paper calls for further large-scale interventional studies designed to determine the role of vitamin D supplementation in the prevention and treatment of PCOS.

## Study limitations

This research provided evidence of a positive correlation between hypovitaminosis D and PCOS. However, the study could not establish a pathophysiological link identifying the trigger lesion in the occurrence of PCOS in patients with low levels of vitamin D.

## Authors' contributions

SSG contributed to the study concept and the analysis and interpretation of data; prepared, drafted, and revised the article; and approved the final draft for publication. K.A, F.M, B.H and R.S contributed substantially to the design of the study. All substantially contributed to the literature

review, acquisition of data, data analysis, production of initial and final drafts, and the approval process of the final draft.

## Conflicts of interest

The authors have no conflict of interest to declare.

## Appendix 1. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jtumed.2017.02.005>.

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