Author’s response to reviews

Title: Association of vitamin D receptor gene variants with polycystic ovary syndrome: A meta-analysis

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Author’s response to reviews:

Editor Comments:

I suggest the authors to consider these papers in their review manuscript:

Krul-Poel YH, Snackey C, Louwers Y, Lips P, Lambalk CB, Laven JS, Simsek S. The role of vitamin D in metabolic disturbances in polycystic ovary syndrome: a systematic review


I also suggest to make revision of the manuscript for English language and grammar (I suggest a revision by an English native speaker).

Response: I have added these papers in the section of discussion. Simsek et al. carried out a systematic review suggested an inverse association between vitamin D status and metabolic disturbances in PCOS. Next, he demonstrated that women with PCOS have a significantly lower serum 25(OH)D compared to fertile controls. A compromised vitamin D status in PCOS women is associated with a higher HOMA-IR and an unfavourable lipid profile. The manuscript for English language and grammar has been revised by an English native speaker.

Reviewer reports:
Roberto Vita (Reviewer 1): The authors have reviewed and meta-analyzed the studies on the association between vitamin D receptor polymorphisms and PCOS susceptibility. They found that only the VDR ApaI (rs7975232) polymorphism and the VDR BsmI (rs1544410) polymorphism associate with PCOS in the Asian population but not in the Caucasian population.

I suggest a careful English proofreading of the whole manuscript. For instance:

* page 3, line 44, "androgen levels";
* page 4, line 14, "by its conversion into the";
* page 4, line 28, "that controls";
* page 5, line 6, "updated";
* page 5, Inclusion and exclusion criteria. Please rephrase;
* page 6, line 9, "constituted by";
* page 6, line 22 "A total score for each study of";
* page 7, line 20 "I2 values of";
* page 7, line 37 "Two-sided P values less than";
* page 8, line 1 "screened";
* page 14, line 20, replace "only" with "and";
* page 14, line 33 "did not include";
* page 14, line 42, replace "do" with "include";
* page 14, lines 44-52, please rephrase;
* page 15, lines 6-12, please rephrase;
* page 15, line 39 ". Further".

* Also, "didn't" in lieu of "did not" is used throughout the manuscript.

Response: Thank you very much for your careful English proofreading. The manuscript for English language and grammar has been revised by an English native speaker.
S. Simsek (Reviewer 2): Xiao-Yuan Shiet al. reviewed an interesting aspect of vitamin D research in the field of polycystic ovary syndrome (PCOS). There are recent important contributions to basic and clinical research including clinical trials. However, the authors have focused on 5 polymorphisms of the VDR gene, from which 3 are variations in intron 8 and 2 are variations in exons.

Forest plots of the VDR polymorphisms should be shown from all the studies not only from the Asian population. In my opinion it is rather an artificial distinction between Caucasian (Egypt, Poland, Australia, Brazil) and Asian (Iran, India, China) populations.

The figures are of very low quality and it is therefore difficult for me to judge them.

Response: We re-analyzed the data and showed the forest plots from all the studies (seen in figure 2).

How certain are the authors that there is no overlap in the studies from Iran?

Page 13 line 50: "Furthermore, on the basis of the pathogenicity of VDR polymorphisms, our research provides a meaningful therapeutic strategy for PCOS." Please clarify!

Response: Reference 16 and reference 17 are the same first author and the association study conducted in Iran. Reference 16 included subjects between July 2011 and September 2012, and reference 17 included subjects between October and June 2006. So there is no overlap in the studies from Iran. "Furthermore, on the basis of the pathogenicity of VDR polymorphisms, our research provides a meaningful therapeutic strategy for PCOS.", we have deleted this sentence.

A cross-ethnic meta-analysis of genetic variants for PCOS (JCEM 2013 Dec; 98(12), Y.V. Louwers et al. did not show linkage with the VDR gene. Please discuss.

Response: We have discussed in the section of discussion. Previous genome-wide association studies (GWAS) of Han-Chinese PCOS patients didn’t reveal VDR gene as new susceptibility loci for PCOS [1,2]. Subsequently, Louwers et al. performed a cross-ethnic meta-analysis of genetic variants for polycystic ovary syndrome[3]. Meta-analysis of the Chinese, US, and Dutch data resulted in 12 significant variants mapping to the YAP1, RAB5B/SUOX, LHCGR, THADA, DENND1A, FSHR, c9orf3, SUMO1P1 loci, but not included VDR gene[3-5].


