## Response to letter by Azziz R., et al 🚥

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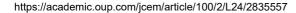
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**Issue Section:** Correspondence

We appreciate the opportunity to respond to the comments and matters raised by Azziz et al regarding our article, "The polycystic ovary syndrome evolutionary paradox: a genome-wide association studies-based, in silico, evolutionary explanation" (1). We thank these authors for their comments and for bringing up a stimulating discussion, which reflects the difficulties in defining clear different polycystic ovary syndrome (PCOS) phenotypes. With this



letter, we have the possibility to better explain our opinion in this regard.

We agree with Azziz et al about the intimate connection of PCOS clinical features, from the androgenic to the metabolic ones. Our intention was to define a prevalent trait for each group, having in mind that the phenotypes of PCOS are hardly separable. This has been summarized at the end of the introductive paragraph of PCOS phenotypic features. The use of the nomenclature, metabolic phenotype and hyperandrogenic phenotype, was aimed at simplifying the comparison of different genetic clusters for an easier presentation of the results.

It is true that any classification of the PCOS phenotypes is itself limited by the wide range of clinical symptoms of this syndrome (2) and the lack of mathematical models for defining them. Even if supported by many authors (2), the suggested differentiation in hyperandrogenic and nonhyperandrogenic forms is, in our

opinion, not fully representative of the global possible phenotypes. As previously suggested (3, 4) and recently remarked by The European Society of Endocrinology (5), our data support an important role of the metabolic changes in PCOS-affected women. We think that the metabolic issue must be added to the nomenclature suggested by Azziz et al (2) in order to better define such a complex syndrome.

In general, all the classifications of human diseases must be carefully taken into account because of the intrinsic nonmathematical nature of the medical science.

Regarding the comment about the previous studies about PCOS and the possible referral and observer bias, we agree that some limits could exist. But we also have to trust the peer-reviewed literature, published in prestigious international journals. The suggestion of developing a statistical system to compensate for this bias is of great interest, and it encourages future studies

about this fascinating and still not completely explored field.

## **Abbreviations**

PCOS polycystic ovary syndrome.

## References

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