Reviewer's report

Title: CYP19A1 and PPARG promoter methylation in saliva associated with milestones of pubertal timing in urban girls

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Reviewer: Jens Vanselow

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In their study, Stueve and colleagues found a statistically significant association of CYP19A1 promoter methylation in saliva with milestones of pubertal timing in girls. They suggest that methylation of this gene in the surrogate tissue saliva may improve risk prediction.

Methodologically, the study seems well performed and that data are appropriately described and presented.

The major problem of the design of study however is the complete lack of any reasonable mechanism, which might be responsible for the claimed connection between CYP19A1 promoter methylation in a very likely non-expressing surrogate tissue (saliva) and the pubertal features investigated. Generally, promoter DNA methylation levels are highly tissue-specific with high levels in non-expressing, but low levels in expressing tissues. Accordingly, there is no reason to assume that the methylation levels in a non-expressing surrogate tissue may have any impact on expression in CYP19A1-active tissues as ovary, adipose tissue etc. Of course, CYP19A1 methylation levels may affect aromatase expression in these tissues, which in turn may increase or decrease E2 production and eventually the onset and characteristic of puberty.

This complete lack of any reasonable mechanistic explanation together with the borderline significance, probably due to relatively low number of samples (<130) makes this study very preliminary and the conclusion of the authors do not seem sufficiently substantiated.

Minor Essential Revisions:
The title should be change, because PPARG methylation did not show any significant association with pubertal timing.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests