RE: Statistical Interpretation Error in Metformin Trial Article

The article by Dr Pastor-Villaescusa may make a valuable contribution to the literature if interpreted correctly. However, in its current form, it contains an important error of statistical inference.

Specifically, the abstract states that "Metformin decreased the BMI *z* score and improved inflammatory and cardiovascular-related obesity parameters in prepubertal children but not in pubertal children. Hence, the differential response according to puberty might be related to the dose of metformin per kilogram of weight."

Yet, in contrast to the statement above, the body of the article states, "No differences were found in the impact of metformin according to the pubertal stage when the interaction time × treatment × puberty was applied to the entire population ($P = .41$)." Furthermore, Table 2 shows that the placebo-corrected reductions in BMI *z* score in the prepubertal and pubertal groups are, within the precision reported in the table, identical.

In short, there is no evidence for a "differential response" by pubertal status, contradicting the authors' conclusion statement. The authors have made a common but serious error of inference by neglecting the fact that "Difference in Nominal Significance is not a Significant Difference," as has been described elsewhere.[1,2]

The conclusion offered by the authors is not supported by the data and should be corrected.

David B. Allison, PhD
University of Alabama at Birmingham
E-mail: dallison@uab.edu

CONFLICT OF INTEREST: The author has indicated he has no potential conflicts of interest to disclose.

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Authors' Response

We thank Dr David B. Allison for his kind comments about the significance of our study and we agree with him about the importance of a correct interpretation of the article.

First, we would like to clarify that by including the phrase "differential response according to puberty" in the abstract, we were not implicitly declaring that there was a significant differential response. We meant that the effect of metformin was noticed in prepubertal children, but not in pubertal children, when compared with the effect of placebo, which we clearly demonstrated by using a general lineal model for repeated measures (GLM-RM) in which each group was analyzed separately. Nevertheless, to avoid having this statement lead to confusion, we agree with changing the conclusion from "Metformin decreased the BMI *z* score and improved inflammatory and cardiovascular-related obesity parameters in prepubertal children but not in pubertal children. Hence, the differential response according to puberty might be related to the dose of metformin per kilogram of weight. Further investigations are necessary." to "Metformin decreased the BMI *z* score and improved inflammatory and cardiovascular-related obesity parameters only in prepubertal children, but a differential effect of metformin was not observed in prepubertal compared with pubertal children. Nevertheless, the doses per kilogram of weight administrated may have had an impact on the metformin effect. Further investigations are necessary."

In this study, we presented 2 independent statistical analyses. The sample size was calculated to ensure 2 equal and matched groups ($n = 80$ for each group), according to the pubertal condition. Hence, in the initial analysis, we separated the prepubertal and pubertal groups in the GLM-RM by using an interaction term for time and treatment. Our assumption was based on the physiologic differences between both pubertal groups, which we consider highly relevant in clinical trials with young subjects. The analyses revealed that the metformin effect was significantly higher than the placebo effect in prepubertal children ($P = .04$), but not in pubertal children ($P = .19$).[1] The difference in effect between the metformin and placebo groups is not a nominal difference because we did not use a within-group approach. We think it is permissible to perform a separate analysis. By stating that "None of the previous studies used a study design to allow observing a differential response by pubertal status separately,"[1] we intend to highlight that we focused the analysis by clearly separating both groups. Actually, the doses per kilogram of body weight were statistically lower in pubertal children ($P < .001$), which could explain why no effect was observed. Hence, we suggested that higher doses for subjects aged 10 to 16 years[2] might improve the design in further trials. Nevertheless, given the lack of studies performed in children on the basis of puberty status, we conducted a second a posteriori analysis including the entire cohort. For this analysis, a GLM-RM that included an interaction term for time × treatment × puberty was used. This analysis demonstrated no different effect of metformin according to pubertal stage ($P = .41$).[1] Indeed, this interaction would suggest that there are no significant differences in the effect of metformin based on pubertal stage.

Second, we would like to clarify that we did not consider placebo-corrected reductions in Table 2, which shows BMI *z* scores compared with placebo

from baseline to 6 months after intervention. We believe that it is not appropriate to only observe the difference of the net reduction of 0.2 points between placebo and metformin in both prepubertal and pubertal groups when a complex model is used, because such models correct means according to the fixed effects included, taking into account several factors that influence the results.

Belén Pastor-Villaescusa
Postdoctoral Researcher, Institute of Nutrition and Food Technology, University of Granada, Granada, Spain
E-mail: mbpastor.ugr@gmail.com

Julio Plaza-Díaz
Postdoctoral Researcher

Concepción M. Aguilera
Associated Professor

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Belén Pastor-Villaescusa, Julio Plaza-Díaz and Concepción M. Aguilera

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