

Methodological considerations in interpreting a synbiotic trial for pediatric functional abdominal pain

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We read with interest the randomized, double-blind, placebo-controlled trial by Arsoy et al. investigating the clinical and immunological effects of a synbiotic in children with functional abdominal pain not otherwise specified (FAPNOS).¹ Randomized controlled trials examining synbiotics in pediatric functional gastrointestinal disorders remain scarce, and the inclusion of a cytokine panel alongside symptom outcomes adds an immunological dimension largely absent from prior work in this age group. We wish to raise several methodological points that bear on the interpretation of the results.

The reporting of interleukin-13 (IL-13) requires closer examination. The authors identify the post-treatment rise in IL-13 within the synbiotic group ($p < 0.001$) as the most notable finding and use it as the primary basis for their conclusions. However, the between-group comparison of post-treatment IL-13 levels did not reach statistical significance ($p = 0.519$). In a randomized controlled trial, the between-group test is the correct inferential comparison. Within-group pre-post changes in a single arm do not establish a treatment-specific effect, particularly when the placebo group showed a directionally similar rise from 0.61 to 0.70 pg/mL. Conclusions built on within-group findings that lack between-group confirmation do not accurately reflect the trial's immunological evidence.²

The question of statistical power also deserves consideration. The rate of symptom reduction was numerically greater in the synbiotic group than in the placebo group (median 100% versus 80%), with a p-value of 0.054. In a trial of 80 participants with a condition characterized by considerable biological heterogeneity, a borderline result of this magnitude may reflect an underpowered sample rather than true equivalence between treatments. No post hoc power calculation was reported, and underpowering is not considered among the study's limitations. Declaring a negative outcome on the basis of a borderline p value, without addressing the possibility of a type II error, limits the conclusions that can be drawn from the symptom data.³

The placebo response rate warrants further discussion. Complete symptom resolution occurred in 43.9% of the placebo group, consistent with the high placebo response rates reported across functional gastrointestinal disorder trials.⁴ Moreover, patients in both groups received weekly telephone contact throughout the 8-week period. In functional pain disorders, structured clinical attention can independently reduce symptom burden through modulation of the gut-brain axis. The placebo condition in this trial therefore incorporated an active psychosocial element, which may have attenuated the detectable



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between-group difference and warrants acknowledgment when interpreting the null symptom outcome.

Psychosocial factors represent a further dimension that was not addressed. The authors' introduction explicitly identifies psychosocial distress as a key driver of FAPNOS. Despite this, no psychological assessment was performed at baseline or follow-up: no anxiety screening, no quality-of-life measure, and no family functioning assessment. In a disorder where gut-brain dysregulation is a primary pathophysiological mechanism, the absence of psychological characterization at enrollment means that the two groups may have differed in an important and unmeasured dimension, limiting the ability to attribute observed symptom changes to the biological properties of the synbiotic.⁵

Finally, the mechanistic basis of the cytokine findings cannot be assessed without gut microbiome data. The rationale for synbiotic therapy in FAPNOS rests on the assumption that modifying microbial composition leads to downstream immune modulation. No stool microbiome profiling was performed, and the observed shifts in IL-13 and interferon- γ within the synbiotic group therefore cannot be connected to any microbiome-level change. The statistically significant rise in transforming growth factor- β in both the synbiotic and placebo groups ($p < 0.001$ in each arm) adds to this uncertainty. A shared immunological trajectory across both study arms points toward a nonspecific temporal effect, the nature of which microbiome data might have helped clarify.

This trial makes a useful contribution to a field where well-designed pediatric studies are few. The randomized design, double-blinding, and inclusion of a multicytokine panel reflect careful planning. Future studies in this area would be strengthened by prospective power calculations, validated symptom assessment instruments, standardized psychosocial evaluation at baseline, and stool microbiome profiling to support mechanistic interpretation of immunological findings. The authors' work provides a constructive reference point from which such studies can be designed.

Author contributions

Conception: P.A.K.; Design: P.A.K.; Data acquisition: H.P.C., P.A.K.; Data analysis: H.P.C., P.A.K.; Data interpretation: H.P.C., P.A.K.; Drafting of the manuscript: H.P.C. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Data availability statement

Data sharing is not applicable to this article as no new datasets were generated or analyzed during this study.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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