

# Comment on Nemet et al.

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To the editor,

We read with great interest the article entitled ‘Food-induced anaphylaxis during infancy is associated with later sleeping and eating disorders’ by Nemet and colleagues<sup>1</sup>. The retrospective study suggests that food-induced anaphylaxis (FIA) diagnosis in the first 3 years of life is associated with an increased risk of developing eating and sleeping disorders in the following average of 6.5 years. We congratulate the authors for their findings; however, several methodological issues should be addressed before applying the result to clinical suggestions.

First, the authors include parameters such as sex, age, ethnicity, and socio-economic status for propensity score matching in Table 1<sup>1</sup>. However, several other factors may lead to potential confounding. Tsai et al.<sup>2</sup> reported familial aggregation of IgE-mediated food allergy and heritability of food-specific IgE, indicating genetic factors may play a role in developing FIA. Pettersson et al.<sup>3</sup> suggested genetic and environmental roles in the etiology of psychiatric disorders. We suggest adding the patient’s family history of psychological disorders (PDs) and food allergies as matching characteristics. Dietary patterns and antibiotic use<sup>4,5</sup> could also contribute to residual confounding.

As the authors stated, one of the limitations is that the study does not include atopic dermatitis and asthma. It is noted that allergic rhinitis should also be considered an important confounding factor<sup>6</sup>. On the other hand, primary caregivers’ strict compliance with children’s diet restrictions and behavioral education could serve as secondary stress for developing psychological disorders<sup>1</sup>. This raises the question of whether the association between FIA and eating and sleeping disorders is due to biological factors or behavioral causes.

In addition, analyzing the patients’ age categories into <3 and 3–18 years could result in heterogeneity of the study population. Gupta et al.<sup>5</sup> reported that a history of skin infection and eczema is associated with an increased prevalence of food allergy. This shows children with different ages of FIA onset may represent varied immune states and biological characteristics. Categorizing 3 to 18 years into one age group could miss information related to health state changes across different ages. We recommend separating the 3 to 18 age groups into preadolescence (4 to 12 years) and adolescence (12 to 18 years) when evaluating controls and patients with FIA, with and without psychological disorders, to minimize population heterogeneity.

The Kaplan-Meier curves in Figure 1<sup>1</sup> showing the incidences of psychological disorders, sleeping, and eating disorders over the study period are questionable. Patients with FIA demonstrate higher cumulative risks of psychological disorders from the beginning, especially for any PDs and eating disorders, implicating the two study groups may have different baseline characteristics. Possible reasons include selection bias and residual

confounding in propensity score matching. Moreover, although the 1:10 referent matching on the propensity score increases statistical power, higher referent matches could narrow the selection of the target population, losing subjects of interest. Thus, it might be inaccurate to transport the average treatment effect on the treated (ATT) of FIA to the unmatched population<sup>7</sup>. This needs to be considered when making generalizable references to the research conclusion.

Finally, this retrospective study includes data from 2001 through 2021, with 20 years of range. We suggest the authors provide secular FIA diagnostic rates across these years. The FIA diagnostic rates may change over time, leading to biased exposure estimates and an underestimation or overestimation of the association between FIA and PDs. Additionally, there has been a steep increase in the prevalence of food allergy worldwide in the past years, indicating that altered dietary patterns and environmental factors could result in different FIA incidences through the years<sup>4</sup>. We suggest the authors divide the 20-year study period into 5-year time blocks to observe exposure changes related to the association of FIA and PDs.

To conclude, the study shows an important result of food-induced anaphylaxis and psychological disorders. We should be careful when evaluating the association between FIA and PDs, the generalizability of the study result, and whether it should be restricted to the Jewish and Arab populations. Finally, health education on FIA management and the psychological well-being of the children and caregivers should hold equal importance as accurately diagnosing FIA.

(680 words)

## References

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