

Author's response



Motivated by the article by Zazzali et al,¹ my editorial² was intended to elaborate on the possibility of having conflicting conclusions concerning clinical significance vs statistical significance. I would like to thank the authors for their constructive letter³ in support of clinical significance of the effects of omalizumab on angioedema in patients with chronic idiopathic/spontaneous urticaria. The statistical significance of the collective primary outcome differences in patients treated with an active intervention compared with a control is often assessed in terms of the difference in the outcome means for the treatments. Interpretation of the statistical significance of this difference may be obscured by inherent variability in individual responses, irrespective of the magnitude of treatment effectiveness. On the other hand, even when the active intervention has no effect whatsoever and a well-designed randomization plan has been used to assign patients to active or control groups, it is possible to find by chance statistical significance. Following traditional statistical procedures, a *P* value is calculated, under the assumption that there is no active treatment effect and the means are in fact identical, to estimate the probability of obtaining a difference in means at least as large as the observed difference. Small differences are expected to yield large *P* values, and large differences are expected to yield small *P* values. However, large differences are expected to be rare if there is no active effect and the underlying population means are identical. Thus, experimental results that yield small *P* values cast doubt on the assumption of identical means used in calculating the *P* value. Typically, differences that yield *P* values that are less than or equal to .05 are defined as statistically significant. However, as noted in my editorial,² differences that are statistically significant are not necessarily clinically significant. For example, if the samples are

composed of large numbers of patients or the variability among patient responses is small, observed differences that are not clinically significant may be deemed statistically significant.⁴ The point of my editorial was not to “advise the readers on the importance of sufficiently large sample size in randomized clinical trials to ensure the outcomes are captured appropriately” but rather to caution against reporting statistical significance without discussing clinical significance. Although clinical and statistical significance are both important, it is my view that investigators often rely too heavily on the statistical significance of their findings and fail to fully develop a discussion of clinical relevance.

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References

- [1] Zazzali JL, Kaplan A, Maurer M, et al. Angioedema in the omalizumab chronic idiopathic/spontaneous urticaria pivotal studies. *Ann Allergy Asthma Immunol*. 2016;117:370–377.e371.
- [2] Johnson WD. Angioedema in the omalizumab chronic idiopathic and spontaneous urticarial pivotal studies: clinical relevance vs statistical significance. *Ann Allergy Asthma Immunol*. 2016;117:339–340.
- [3] Zazzali JL, Kaplan A, Maurer M, et al. Importance of angioedema-free days in patients with chronic idiopathic/spontaneous urticaria. *Ann Allergy Asthma Immunol*. 2017;118: 524.
- [4] Ziliak S. *P*-values and the search for significance. *Nature Methods*. 2017;14:3–4.

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Re: “Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases—sponsored expert panel”



The Learning Early About Peanut Allergy (LEAP) Study has shed light on a growing prevalence of allergy to peanuts. The trial concluded that early exposure to peanuts in a child's diet decreases the frequency of developing peanut allergy.¹ Based on this trial and expert opinion, the new addendum guidelines^{2–4} help tailor the introduction of peanut into the diet of children who are at high risk of developing allergy. Although decreasing the incidence of severe peanut allergy is of significant importance, the public has to be equally aware of the danger of allowing the ingestion of solid peanuts in children younger than

2 years because of the risk of aspiration. Foreign body aspiration is very common, with potentially fatal outcomes in young children. In a meta-analysis published in 2012, organic foreign bodies, specifically nuts, were found to be the most commonly inhaled objects.⁵ If not removed in a timely manner, the aspirated peanut in the airway can cause serious complications, ranging from pneumonia to death.⁶ It has been estimated that the combined rate of anoxic brain injury and death from foreign body aspiration is 4%.⁷

Furthermore, airway foreign body aspiration is associated with a significant burden on the health care system. In the United States, almost \$13 million is spent annually on inpatient costs for the

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management of foreign body aspiration in children.⁷ This does not include costs related to outpatient care.

The LEAP Study guidelines recommend the introduction of peanut protein into the diet of young children. This recommendation must consider the risk of aspiration in young children exposed to solid peanut products. For that reason, peanut allergy prevention programs should run hand in hand with a concerted effort to educate parents about the risk of solid peanut ingestion in younger children.

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References

- [1] Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372:803–813.
- [2] Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases—sponsored expert panel. *Ann Allergy Asthma Immunology*. 2017;118:166–173.e7.
- [3] Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases—sponsored expert panel. *Pediatr Dermatol*. 2017;34:e1–e21.
- [4] Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases—sponsored expert panel. *J Allergy Clin Immunol*. 2017;139:29–44.
- [5] Foltran F, Ballali S, Passali FM, et al. Foreign bodies in the airways: a meta-analysis of published papers. *Int J Pediatr Otorhinolaryngol*. 2012;76(suppl 1):S12–S19.
- [6] Foltran F, Ballali S, Rodriguez H, et al. Inhaled foreign bodies in children: a global perspective on their epidemiological, clinical, and preventive aspects. *Pediatr Pulmonol*. 2013;48:344–351.
- [7] Kim IA, Shapiro N, Bhattacharyya N. The national cost burden of bronchial foreign body aspiration in children. *Laryngoscope*. 2015;125:1221–1224.