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Reply

To the Editor:

Kazaks et al¹ describe an interesting independent data set confirming the association between levels of exhaled nitric oxide (eNO) and body mass index (BMI) in healthy adults as we reported in the Journal.² Recently, Buchvald et al³ added further support for such an association in healthy children between 4 and 17 years of age. In their study eNO levels were significantly related to height and weight.

Another important finding of Kazaks et al¹ is the significant association between serum leptin levels and eNO in healthy controls. Leptin is the protein of the putative obesity gene and has been shown to upregulate the inflammatory immune response.⁴

In a group of patients with asthma, the authors described considerably higher levels of eNO, but no association between BMI and eNO levels was observed. In patients with asthma, eNO levels are highly variable and are strongly influenced by anti-inflammatory therapy.⁵ Kazaks et al¹ do not describe the therapy regimen in their patients, but obviously the variability in eNO levels in patients with asthma surpasses the obesity-related effects.

Up to now, combined data from the literature have shown an epidemiological association between asthma and obesity and an association among obesity, leptin, and eNO. It remains to be established whether this is a result of common (genetic or inflammatory) pathways or causal relationships. The striking effect of both emerging entities on current medical health care systems justifies further unraveling of these intriguing pathogenetic pathways. Perhaps diseases like cystic fibrosis, combining poor nutritional state with low eNO levels, can offer helpful clues. For these reasons, we believe that the observations of Kazaks et al¹ in patients with prevalent asthma do not preclude the possibility that the association between BMI and eNO plays a role in the incidence of asthma.

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Atopic characteristics of children with recurrent wheezing at high risk for development of childhood asthma

To the Editor:

The investigators of the Prevention of Early Asthma in Kids (PEAK) Trial are providing a valuable study of importance to physicians and families.¹ The recent publication of the atopic characteristics of the children enrolled in the study provides important insights.¹

However, we were concerned with some discrepancies of subject enrollment and statements of asthma status. We noted several inconsistencies.

In the Methods, the authors state that they will "focus on API [Asthma Predictive Index] major criteria revealed in the Tucson Children's Respiratory study cohort in this analysis;" but in the Results, they state, "Of the 244 participants, 90.3% met the mAPI [Modified Asthma Predictive Index] criteria." Furthermore, the authors state in the Discussion, "In this analysis we examined a young group of children with frequent wheezing and at least one of the 2 major criteria of the API." Could the authors clarify which API criteria are being used, the mAPI or the original API?

In the Methods, the authors state, "Children 2 and 3 years of age with frequent intermittent wheezing at high risk of persistent asthma but without persistent symptoms were identified by meeting the criteria for a positive mAPI result." However, in the Discussion, they state, "PEAK, therefore has the potential to examine the atopic and asthmatic characteristics of a high-risk cohort with frequent intermittent wheezing episodes who are likely to have persistent asthma." If they were at risk for asthma but without persistent symptoms, why state that they are likely to have persistent asthma?

The same phrase in the introduction, "Children 2 and 3 years of age with frequent intermittent wheezing at high risk of persistent asthma but without persistent symptoms," contrasts with a statement made in the Results: "with an age of physician diagnosis of asthma of 16.0 + 9.9 months in 86% of participants who had received this diagnosis." Are they at risk for asthma, or do they already have asthma?

A statement made in the Discussion, “PEAK therefore has the potential to examine the atopic and asthmatic characteristics of a high-risk cohort with frequent intermittent wheezing episodes who are likely to have persistent asthma,” contrasts with a later statement: “PEAK cohort represents a cohort similar to the CAMP cohort but before persistent asthma has developed.” Has persistent asthma developed or not?

The information presented in this article will be of critical importance. However, we thought the inconsistencies noted distracted from the critical message of the article and left us guessing about some of the details of the study design.

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Reply

To the Editor:

We thank Dr Hopp¹ for his thoughtful response to our recent article, which allows us to explain the intent of our study better. He raises 2 main objections concerning the inclusion of modified asthma predictive index (mAPI) characteristics in the Results section and whether the children enrolled in the study have persistent asthma.

The original asthma predictive index (API) was based on data from the Tucson Children's Respiratory Study (TCRS).^{2,3} The API included frequent wheezing in the first 3 years of life and either 1 major risk factor (parental history of asthma or personal history of atopic dermatitis) or 2 of 3 minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis).³ Because allergic rhinitis can be difficult to diagnose in young children without immunologic confirmation, the published API was modified for use in the Prevention of Early Asthma in Kids (PEAK) study (mAPI) to include allergic sensitization to aeroallergens as a major criterion and substitute for allergic rhinitis. Food sensitization was added as a minor criterion because its presence has been reported to be predicted for the development of asthma (references in article). The analysis in this article focused on the API and mAPI major criteria, which are the same for both indices: a parental history of asthma, a personal history of atopic dermatitis, or both. Because the children were enrolled in PEAK based on a mAPI, not the original API, we thought it was more accurate to use mAPI within the results section. This designation also allows us to report the frequency of all 3 major criteria of the mAPI within the cohort.

Regarding the second comment, persistent wheeze is defined in the TCRS as wheeze that was present in both the

first 3 years of life and at 6 years. It does not, however, imply persistent asthma symptoms as described in the National Asthma Education and Prevention Program guidelines. Thus, intermittent wheezing in the preschool years can represent many different disease phenotypes, and intermittent wheezing by itself does not predict which children will have continuation or persistence of wheezing in the older school years. If fact, 60% of children who begin wheezing at age younger than 3 years will outgrow their disease by age 6 years (transient wheezers) and an additional 20% by age 13 years (nonatopic wheezers).^{2,4} Thus, a physician diagnosis of asthma alone does not necessarily identify children who will continue to wheeze during the school years. The children in this cohort also had an average onset of wheezing at age 11.2 months (Unpublished data, Guilbert TW, November 2004). Their disease cannot be considered persistent because they still may outgrow their wheezing symptoms by age 6 years. However, using the TCRS data, the API identifies children at 4.3 to 9.8 times the risk of having continued wheezing or asthma during the school years.³ The children enrolled in the PEAK study have wheezing that is episodic and of short duration; thus, we must conclude that they do not yet have persistent disease but are at high risk to develop it.

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β -Blockers and anaphylaxis: Are the risks overstated?

To the Editor:

In the recent updated practice parameter for the diagnosis and management of anaphylaxis, the panel states that