

Moreover, we think that in the study conducted by Westerhof et al, some important confounders such as body mass index and smoking were considered as *fixed* confounders in the analysis. In other words, there is a degree of residual confounding in the association between nasal polyps and airway hyperresponsiveness with persistent asthma. These confounders are mainly *time-varying* confounders and *time-modified* confounders. Time-varying confounding means that the *value* of the confounder changes over time, whereas *time-modified* confounding means that the *effect* of the confounder changes over time. *Time-modified* confounders have been considered in the Epidemiology and Biostatistics literature and some methods have been introduced to address them in the analysis.<sup>4</sup>

A take-home message for the readers is that because of lack of validation in the study and the presence of residual confounding, the effect of nasal polyps and airway hyperresponsiveness on persistent asthma should be interpreted with caution.

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## Reply



To the Editor:

We thank Ayubi and Safiri<sup>1</sup> for their commentary on our recently published article “Clinical predictors of remission and persistence of adult-onset asthma.”<sup>2</sup> In this study, we found that moderate to severe bronchial hyperresponsiveness and nasal polyps were independent predictors of asthma persistence.<sup>2</sup>

At first, Ayubi and Safiri raise concern about the lack of predictive performance testing, which might lead to overfitting of the final model in our study.<sup>2</sup> However, it was not the aim of our study to test the predictive performance of a prediction model. The main goal of our study was to identify baseline predictors of adult-onset asthma remission and persistence after 5-year follow-up. Therefore, we used logistic regression analysis to identify baseline factors associated with the outcomes persistence or remission. After selection, bronchial hyperresponsiveness and nasal polyps appeared to be the only independently associated factors with asthma outcome. To offer a clinically useful interpretation of this finding, we constructed a prediction formula

that can be used to estimate the chance of asthma remission for a patient with newly diagnosed asthma. This model might indeed be more optimistic than a validated model, but this does not challenge the relevance of nasal polyps and bronchial hyperresponsiveness in determining asthma outcome.

Second, Ayubi and Safiri<sup>1</sup> comment on the use of fixed confounders instead of time-varying and time-modified confounders. In the logistic regression we used fixed baseline factors that were measured shortly after asthma diagnosis. Whether these factors change over time does not matter for the association between a baseline factor and the outcome after 5 years. However, we do think that the change in (confounding) variables might be of interest; therefore, in our futures analyses we will take longitudinal changes into account, for example, change in FEV<sub>1</sub> or fluctuations of inflammatory markers.

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## Timing of regular egg intake for prevention of egg allergy



To the Editor:

We read with great interest the articles titled “Randomized placebo-controlled trial of hen’s egg consumption for primary prevention in infants” by Bellach et al<sup>1</sup> and “Randomized controlled trial of early regular egg intake to prevent egg allergy” by Palmer et al.<sup>2</sup> Both the excellent studies investigated the efficacy of regular consumption of egg protein from age 4 to 6 months on the reduction of egg allergy. Both of them failed. According to the theory of infant immunotolerance induction, the failure of these studies might be caused by the timing of regular egg intake.

Design of the clinical intervention to prevent allergic disease shall be based on the understanding of the mechanism of immunotolerance to external antigens of infants. After delivery, infants have to face massive external antigens. Thus, the immune system of the infant needs to balance 2 different jobs: immunotolerance to massive safe external antigens and prevention of infection. Infants live in a relatively safe environment with low level of pathogens due to the protection of parents. Thus, the major job of infant immune system is to induce immunotolerance to external antigens. The mechanism of this tolerance is still controversial. Studies indicated that the T<sub>H</sub>1/T<sub>H</sub>2 balance was

different among children and adults.<sup>3</sup> Children tended to present to T<sub>H</sub>2 priority, which was considered the mechanism of immunotolerance of infants. However, overactivation of T<sub>H</sub>2 caused allergic diseases including asthma.<sup>4</sup> Thus, T<sub>H</sub>1/T<sub>H</sub>2 balance might not be the key inducer of immunotolerance. Recently, 2 novel immunosuppressive cells in infants, CD71<sup>+</sup> erythroid cells<sup>5</sup> and regulatory T cells,<sup>6</sup> were found to play critical roles in inducing immunotolerance to external antigens and help the colonization of microbiota in intestine and skin. The 2 novel mechanisms highly suggested that immunotolerance of infants was induced by the immunosuppressive cells, which presented T-cell sensitization to safe external antigens. Notably, these cells only exist shortly after birth, which indicated the key window for immunotolerance induction, first weeks after birth. Thus, to prevent egg-related allergic disease, the regular egg intake shall be started shortly after birth by being added to milk.

All in all, based on the recent understanding of infant immunotolerance to external antigens, regular egg intake shall be a promising method to prevent egg allergy. However, the treatment was too late for 4- to 6-month infants. The studies shall be redesigned and regular egg intake shall be started shortly after birth by being added to milk.

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## Reply

To the Editor:

Jiang et al<sup>1</sup> have raised an important question with regard to our recent randomized controlled trial (RCT) investigating early

regular egg intake to prevent egg allergy in infants without eczema.<sup>2</sup> Our findings in this recent RCT, along with those in our previous RCT “Early regular egg exposure in infants with eczema: a randomized controlled trial”<sup>3</sup> and those of Bellach et al,<sup>4</sup> all demonstrate that a significant proportion of infants have allergic reactions, including anaphylaxis, on first introduction of egg in solid foods as early as age 4 months.

In our human *ex vivo* studies, we have confirmed that elevated egg allergen-specific T<sub>H</sub>2 cytokine responses at age 4 months predict egg allergy at 12 months.<sup>5</sup> These proallergic responses were established before known ingestion of egg in solid foods and were not altered by the timing of subsequent introduction of egg in the infant diet. This confirms the development of egg-specific immune responses before the commencement of infant dietary egg intake around age 4 to 6 months. Thus, to be more effective, we agree with Jiang et al<sup>1</sup> that primary prevention strategies must commence much earlier in immune development before these allergen-specific responses are established.

We do not support exposure to food allergens by introducing solid foods to the baby before age 4 to 6 months because this interferes with exclusive breast-feeding and may have other negative health consequences to the baby. However, food allergens secreted in breast milk are likely to be an important early source of oral food allergen exposure during infancy. In animal studies, allergen exposure through maternal milk has been shown to induce oral tolerance.<sup>6</sup> We have demonstrated that the amount of maternal consumption of egg during lactation influences egg protein (ovalbumin) detection and concentration in human breast milk.<sup>7</sup> Of particular relevance to this discussion is our recently completed RCT investigating whether higher intake of egg in the maternal diet during the first 6 weeks of breast-feeding could modify infant immune responses. Importantly we found that infant egg-specific IgG<sub>4</sub> levels were positively associated with maternal egg ingestion during early lactation.<sup>7</sup> We are now continuing this line of investigation with another new study investigating a longer duration of maternal diet intervention period while breast-feeding. Future research in this field should focus on investigating whether higher maternal dietary intakes of food allergens, such as eggs and peanuts, during pregnancy and lactation can protect from childhood food allergy.

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