

Correspondence: Association of Serum Vitamin D Levels and Recurrent Wheezing in Children

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Dear Editor,

We read with great interest the article titled "Association of Serum Vitamin D Levels and Recurrent Wheezing in Children" by Khan A et al., which has been published in your esteemed journal [1]. We want to share a few of our thoughts regarding this article. The authors did an admirable job by looking at association of serum vitamin D level with recurrent wheezing in children, which is, in fact, a very emerging area of research.

First, authors had taken blood sample for control from healthy infants however, it is not ethically correct to draw blood samples from healthy children.

Second, in this study authors had shown that mean serum levels of vitamin D3, calcium and phosphate were significantly higher in controls compared to cases. However, it could be due to presence of confounders like vitamin D3 and calcium supplementation in control group as they might be regularly visiting the health care facilities for routine check-up and we are aware that vitamin D3 supplementation in first year of life is now standard of care. The authors should have taken account of vitamin D3 supplementation in both case and control.

Third, authors had shown that serum vitamin D level below 17.5 ng/mL predisposes for the recurrent wheezing episodes and decrease in its level by 1 ng/mL in serum, increases the chances of wheezing by 7.3%. However, the sample size is not sufficient to make this conclusion and also longitudinal studies have shown that several factors are responsible for development of recurrent wheezing or asthma in preschool children viz., infection, environmental, genetics, nutrition, history of atopy etc., and most of the time more than one factor is responsible for them [2]. It has also been shown that children who wheeze before three years of age, about 50% of them stop wheezing by six years of age [3]. Hence, recurrence of wheezing is determined by several factors which in turn, direct the particular temporal pattern.

Fourth, for predicting recurrence wheezing we need to consider other factors too viz., serum total IgE, allergic sensitisation, cytokines, maternal vitamin D3 level, pulmonary function test, biological marker etc., [4].

Fifth, authors had observed that breastfeeding rates were significantly higher in wheezing children compared to controls and they concluded that breastfeeding doesn't seem to protect against recurrent wheezing. Systematic reviews have shown mixed effect on association of breastfeeding with asthma, as some of them have shown a clear benefit of breastfeeding, associated with 30% reduced odds of childhood asthma while other didn't observe any association with asthma [4,5]. However, even if there is no direct association of breastfeeding with asthma, there is strong evidence in protective effect of breastfeeding against respiratory infections which are now considered as important predisposing factors for development as well as recurrence of wheezing in preschool children [5].

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AUTHORS' REPLY

We thank the authors for showing interest in the present article [1]. The clarifications to the concerns raised are as follows:

1. This was a case-control study in which sample from healthy control was deemed necessary. The sample was taken after taking written informed consent from one of the parents. As per revised "National Ethical Guidelines for Biomedical Research Involving Children," [2], it falls under the category of "Minor increase over minimal risk or Low risk", which is ethically acceptable. Also, as per the Indian Council of Medical Research (ICMR), this study falls in the Conditions for research on children category. Hence, taking the blood sample in healthy individuals was justified and was in the concordance of revised ICMR guidelines on ethics in human research.
2. We agree with authors that the differences in the biochemical parameters may be due to the differential calcium and vitamin D supplementation. However this doesn't affect the results. We showed that the low levels of vitamin D (despite supplementation if any) are associated with recurrent wheezing. If we assume that more of the babies in the control group were getting supplementation and had higher levels; hence, lower wheeze, then also it strengthens the present finding and advocates routine supplementation as discussed by us.

3. The sample size was adequate for the primary outcome. Logistic regression of the data shows that after adjusting for all other potential confounders; the decrease in 25 hydroxy vitamin D levels by 1 ng/mL, will independently increase the chances of wheezing by 7.3%. We agree that multiple factors interplay in wheezing of which many cannot be adjusted by matching and regression. Larger multi-ethnic and multicentric studies taking all confounders into account will be more productive. As stated by authors, the children who wheeze before three years of age, about 50% of them will still be symptomatic and hence, it has long-term implications too.
4. We agree that many other factors need to be considered while predicting recurrent wheezing. Definitely larger studies encompassing serum total IgE, cytokines, pulmonary function test, and the biological marker will be useful.
5. The present study, as well as recent systematic review involving high-quality studies [3], showed that breastfeeding is not protective against eczema, food allergies or asthma.

Although breastfeeding is known to reduce the incidence of severe lower respiratory tract infections by 57%, the same was not replicated in the reduction of asthma or allergy. Means, the protective effect of breastfeeding on prevention of respiratory infections is not translating in the prevention of reactive airway diseases. This again strengthens the point that there is just an association (may not be a causal relationship) between respiratory tract infections and recurrent wheeze.

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