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Letter to the Editor

Low serum soluble ST2 level in early childhood is associated with the risk for asthma at 7 years of age

Dear Editor,

Asthma is a common chronic inflammatory disease that starts usually in childhood and tends to cause long-term health consequences and negatively affect children's and their families' life quality. Childhood asthma is often associated with T helper (Th) 2 cell response. Interleukin (IL)-33 is an IL-1 family cytokine which signals via suppression of tumorigenicity 2 protein (ST2) receptor.[1,2] The soluble form of ST2 (sST2) acts as a decoy receptor competing with membrane bound ST2.[3] Both IL-33 and sST2 have been shown to be crucial in mediating an allergic airway inflammation, and elevated levels of serum IL-33 and sST2 have been reported in children and adults with asthma.[4]

We aimed to study if the levels of serum IL-33 and sST2 in early childhood are associated with the later development of asthma in children. This study was conducted within the prospective observational birth-cohort study called Steps to the Healthy Development and Well-being of Children (STEPS).[5] The STEPS study is a population-based birth-cohort study which consists of 1827 children born in the Hospital District of Southwest Finland between January 2008 to April 2010 and their families and of these 923 children were included to the intensively follow-up group for respiratory tract infections. In this substudy, we included 146 children whose 13-month serum samples and follow-up data were available. Children were followed intensively from birth to two years of age and after that with annual questionnaires and collection of health registry data. Physician-diagnosed asthma at 7 years of age was defined as a diagnosis of asthma in the medical records or an electronic prescription of inhaled corticosteroids for asthma.[6] Nasopharyngeal and blood samples were collected during prescheduled visits at three time points in early childhood (at 2, 13 and 24 months of age).[5] In this study, sera collected at 13 months were used. Characteristics of the study subjects are presented in Table 1.

Serum IL-33 was determined by multiplex immunoassay (Bio-PLex 200, Bio-Rad Laboratories, Hercules, CA, USA) with MILLIPLEX Th17 Kit (Merck & C0., Kenilworth, NJ, USA), and serum sST2 with the ELISA kit (Elabscience Biotechnology, Wuhan, China). The detection limits of IL-33 and sST2 were 6.3 pg/mL and 190 pg/mL, respectively.

Statistical analyses were performed using SPSS software, version 28.0 (IBM Corp., Armonk, NY, USA). The non-normally distributed data were compared by Mann–Whitney U test and the association between risk factors and asthma development was analysed by binary logistic regression analysis. Sex, delivery mode, existence of older siblings, duration of breast-feeding, child's atopy and parental asthma were included as confounders in the multivariable model assessing the association between serum levels of sST2 and IL-33 at 13 months of age and asthma at 7 years of age. Two-tailed $P < 0.05$ was considered significant.

The serum levels of sST2 varied from 85 to 13626 pg/mL, with a median of 4567 pg/mL (IQR 2714–6111 pg/mL) and levels of IL-33 from 3.1 to 2608 pg/mL, with a median of 12.4 pg/mL (IQR 3.1–44.5 pg/mL). No correlation was observed between serum IL-33 and sST2. Significantly lower level of serum sST2 was observed in children who had asthma at seven years of age (2430 pg/mL, IQR 1755–3475 pg/mL) compared to those without diagnosis of asthma (4803 pg/mL, IQR 3019–6275 pg/mL) ($P = < 0.001$) (Fig. 1A). In addition, the logistic regression analysis showed significant difference between serum sST2 levels between the two groups (OR, 0.999; 95%CI 0.99–1.00) ($P = 0.008$), when six confounders (sex, delivery mode, existence of older siblings, duration of breast-feeding, child's atopy and parental asthma) were included. No difference in levels of IL-33 (OR, 0.995; 95%CI 0.974–1.017) ($P = 0.648$) was found between children with asthma at seven years of age and those without (Fig. 1B).

Table 1
Characteristics of the study cohort.

Characteristics	Total, n = 146 (%)	Asthma at age of 7 years	
		Yes, n = 15 (%)	No, n = 131 (%)
Sex			
Female	69 (52.7)	6 (40.0)	63 (48.1)
Male	77 (47.3)	9 (60.0)	68 (51.9)
Mode of delivery			
Vaginal	121 (82.9)	8 (53.3)	113 (86.3)
Caesarean section	25 (17.1)	7 (46.7)	18 (13.7)
Breastfed over 2 months	122 (83.6)	8 (53.3)	114 (87.0)
Missing data (% from total n)	5 (3.4)	3 (20.0)	2 (1.5)
Atopy at age of 13 months	23 (15.8)	2 (13.3)	21 (16.0)
Missing data (% from total n)	8 (5.5)	1 (6.7)	7 (5.3)
Recurrent Wheezing	21 (14.4)	8 (53.3)	13 (9.9)
Missing data (% from total n)	1 (1.4)	0 (0.0)	1 (0.8)
Parental asthma	18 (12.3)	4 (26.7)	14 (10.7)
Presence of older siblings at time of birth	60 (41.1)	7 (46.7)	53 (40.5)

Data are presented as numbers (n) of children and percentages (%). The diagnose of asthma at age of 6.5–7.5 years were retrieved from medical records of the Hospital District of Southwest Finland and all asthma diagnoses and prescriptions were made by attending physicians. Atopy was defined as doctor-diagnosed atopy by age 13 months.

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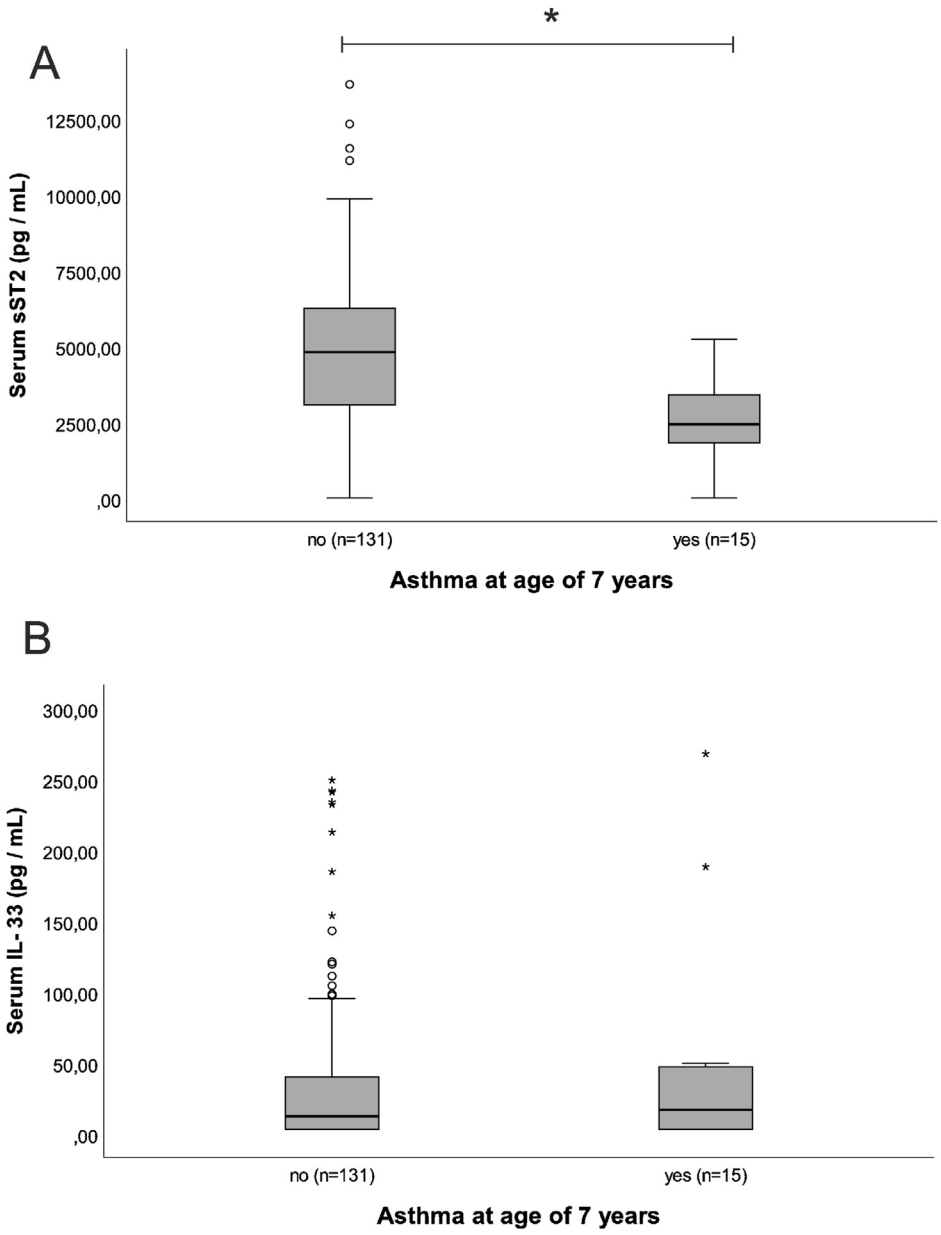

Fig. 1. Comparison of serum sST2 (**A**) and IL-33 (**B**) levels at 13 months of age between children with and without asthma at age of 7 years. Children who had asthma at age of 7 years had significantly lower level of sST2 at age of 13 months (2430 pg/mL, IQR 1755 − 3475 pg/mL) (*P = < 0.001) compared to those without diagnosis of asthma (4803 pg/mL, IQR 3019 − 6275 pg mL). No significant difference was found in serum levels of IL-33 (P = 0.648). Data was analysed by Mann-Whitney U test and two-tailed P<0.05 was considered significant.

In maturated immune system IL-33 is abundantly expressed almost in all human tissues and the expression can be further increased during inflammation or allergen stimuli. Binding of IL-33 to ST2 receptors, expressed on several lung cell types, leads to activation of Myd88 signalling pathway and results in secretion of Th2 cytokines such as IL-13 and IL-5. It is known that sST2 is spontaneously expressed in lung alveolar and bronchus epithelial cells and cardiac myocytes and is lack of transmembrane and intracellular domains of ST2.[3] Previous studies have shown that lipopolysaccharides (LPS) stimulation induces a boost of inflammatory cytokines (IL-6 and TNF-α) that leads to increased NFκB-dependent sST2 secretion in alveolar epithelial cells and cardiac myocytes.[7] Elevated levels of sST2 were reported in patients with different diseases or conditions such as asthma, septic shock, trauma, and cardiovascular diseases.[7] It appears that the appropriate amount of blood sST2 can prevent uncontrolled inflammation via neutralizing its ligand IL-33.[7]

However, accumulating evidence suggests that in un-maturated immune system, especially in lung postnatal alveolarization phase, the high expression of sST2 is shown to be associated with protection of asthma.[8,9] Recently Kaur *et al.* found that bronchial epithelial ST2 protein expression was significantly decreased in biopsies in subjects with asthma compared to healthy controls.[10] In this study, we found that children at about one year of age who were diagnosed with asthma at age of 7 years had significantly lower levels of serum sST2 compared to those who did not develop asthma later. Our result is in line with the findings in which sST2 had strong preventive effect on asthma development in the neonatal period of

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mice[8] and were negatively predicted asthma with high FeNO in preschool wheezers (2–3 years).[9]

In our study, we found that the serum levels of IL-33 were nearly equal in children who later developed asthma and those who did not.

There are some limitations in this study. First, the number of study subjects was limited. Secondly, of 15 children who developed asthma at 7 years of age, three had missing data of duration of breast-feeding and one had missing value of child's atopy and therefore only 12 asthmatic children were included in the logistic regression analyse. However, it should be kept in mind that the OR was close to 1, that makes the clinical significance of study uncertain.

In conclusion, serum sST2, but not IL-33 at early age is associated with higher risk for development of asthma in Finnish children. Our results warrant further studies on the role of sST2 on development of asthma in different populations with large number of subjects.

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Conflict of interest

The authors have no conflict of interest to declare.

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